

BIOMARKERS OF VENTRICULAR REMODELLING IN AFRICAN HYPERTENSIVES

A thesis submitted to the Faculty of Medicine, University of Cape Town, for the
degree of Doctor of Philosophy

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Declaration of originality

I declare that this thesis is my own unaided work. It is being submitted for the degree of Doctor of Philosophy in the Faculty of Medicine, University of Cape Town, Cape Town. The work contained in this thesis has not been submitted for any degree or examination in this university, or any other university

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Declaration of ethical clearance

I hereby certify that the study contained in this thesis has the approval of the Ethical Committee of the University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria. The ethics number is: UATH/HREC/PR/233

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LIST OF ABBREVIATIONS

BNP= Brain Natriuretic Peptide

CH= Concentric Hypertrophy

EH= Eccentric Hypertrophy

CR= Concentric Remodelling

DALYs= Disability Life Years

EDD=End Diastolic Diameter

ESD= End Systolic Diameter

HT= Hypertension without LVH or heart failure

HHF=Hypertensive Heart Failure

HTLVH= Hypertension with LVH but no heart failure

IVSDd= Interventricular Septal Diameter at end diastole

LAA=Left Atrial Area

RAA= Right Atrial Area

LV=Left Ventricular

LVF=Left Ventricular Failure

LVH=Left Ventricular Hypertrophy

LVM=Left Ventricular Mass

ME= Early Mitral Filling of the Left Ventricle

MA= Atrial Filling of the Left Ventricle

NT= N- Terminal

PWDd= Posterior Wall Diameter at end diastole

RAP= Right Atrial Pressure

RVSP= Right Ventricular Systolic Pressure

TAPSE= Tricuspid Annular Plane Systolic Excursion

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DEDICATION

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1 Abstract

There is substantial evidence that the burden of hypertension, hypertension with left ventricular hypertrophy and hypertensive heart failure is very enormous in sub-Saharan Africa. There is therefore the need to look for easier and faster means, compared to electrocardiography and echocardiography of diagnosing and differentiating the different effects of long standing hypertension on cardiac remodelling which ultimately lead to systolic and diastolic dysfunctions as this affects the prognosis, management and treatment modalities of hypertension. We studied 210 subjects who were subdivided into three groups after echocardiography: those without left ventricular hypertrophy (HT) (n=83); those with left ventricular hypertrophy (HTLVH) (n=50) and those with hypertensive heart failure (HHF) (n=77). The subjects had a mean age of 52.3 ± 11.3 years, and the female subjects constituted 42.4% of the study population. HTLVH had the highest levels of mean arterial blood pressure and pulse pressure among the cohort of 120.6 ± 26.7 mmHg and 67.0 ± 26.9 mmHg respectively.

HTLVH had both significantly higher inter-ventricular and left ventricular posterior wall hypertrophy thickness when compared with HT and HHF subjects, p-values < 0.001 respectively, while Subjects with HHF had the highest chamber diameters apart from the right atrial area. Subjects with HHF had higher plasma ST2 concentrations compared to HTLVH ($134.7 \text{ pg/ml} \pm 57.3 \text{ ng/ml}$ versus $23.0 \text{ ng/ml} \pm 8.3 \text{ pg/ml}$, p-value < 0.0001) and those with HT (134.7 ± 57.3 versus 14.5 ± 4.9 , p-value < 0.0000). NT-pro BNP levels were similar when HTLVH was compared with HT (p=0.68), but subjects with HHF had significantly higher NT-pro BNP compared to HTLVH (p<0.0002) and HT (p<0.0001). Also on head-to-head comparison using differences in areas under the curve, ST2 was found to be a better biomarker than NT-pro BNP in differentiating HT from HHF (p<0.0001) and HTLVH from HHF (p=0.01). Serum ST2 is a powerful biomarker in differentiating the different spectrum of hypertension. It does not only complement the role of NT-pro BNP in this regard, but is a superior biomarker.

CHAPTER 1

1.0 Introduction

Hypertension or high blood pressure is a very important worldwide public health problem because of its high rate of occurrence and concomitant risk of cardiovascular, cerebrovascular and kidney disease (He et al 1997; Whelton 1994). Hypertension has been identified as the leading risk factor for mortality. In the latest global burden of disease survey (Lim et al 2012), hypertension is ranked as the leading risk factor for poor health in 2010, as against the fourth leading risk factor for poor health in 1990 (Figure 1.1: Five Leading Risk Factors for Poor Health in 1990 and 2010; Adapted from GBD Project 2010).

The importance of high blood pressure as a major cause of common serious disease has been recognised in most Western countries for over 50 years (Harrington M et al 1959). Before this, malignant hypertension was a frequent reason for hospital admission and a common cause of death. Safe and effective anti-hypertensive drugs were first developed in the 1960s and were shown to dramatically improve the prognosis associated with malignant hypertension (Yu et al 1960). Subsequently, the provision of blood pressure lowering treatments to a much broader group of patients at risk of serious cardiovascular diseases, such as cerebrovascular accident and coronary heart disease, importantly contributed to the decline in stroke and coronary heart disease death rates experienced by most Western populations (Unal et al 2005). However, in contrast to higher-income countries, the burden of hypertension and hypertension-related diseases increased in lower-income countries. This has been attributed to increasing urbanisation (Singh et al 2000).

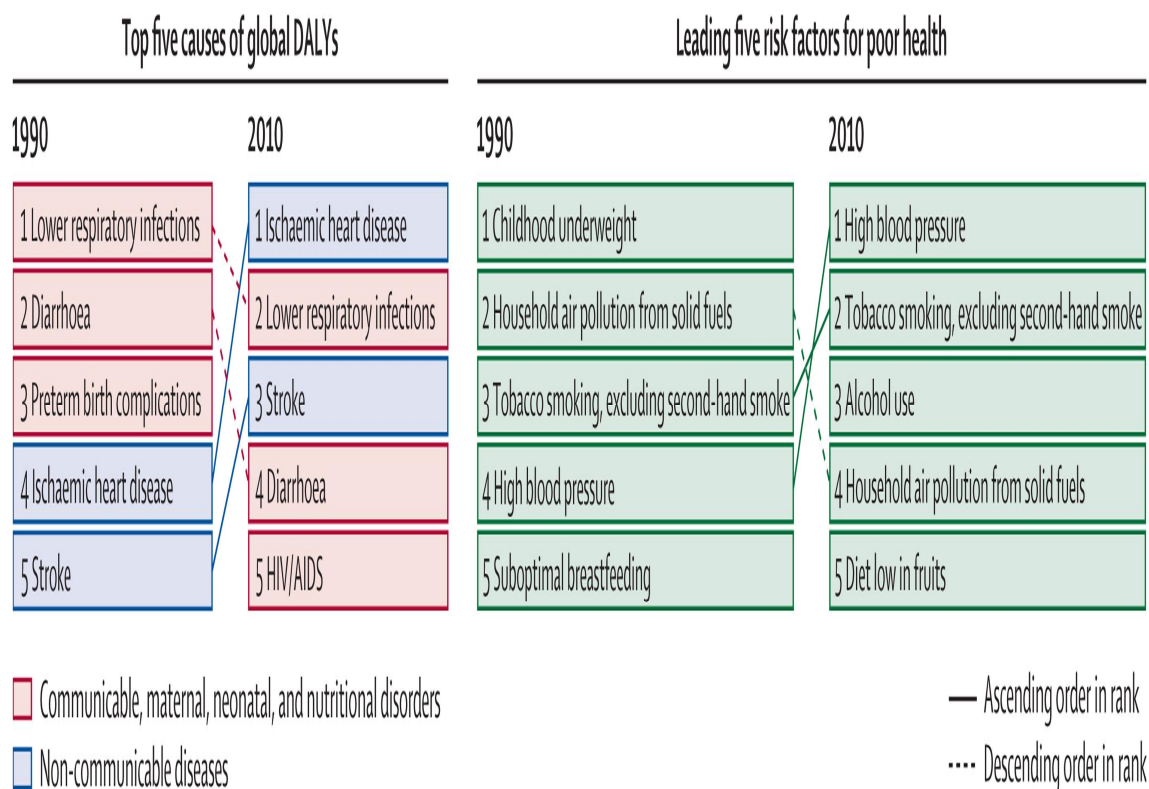


Figure 1.1: The main causes of global DALYs and top five risk factors for poor health in 1990 and 2010(adapted from GBD Project 2010)

1.1 Definition of Hypertension

The cut-off mark for the definition of hypertension has evolved over time. The current definition is that of the Seventh Joint National Committee Report (JNC7) which defines three levels of elevated blood pressure (Chobanian et al 2003). These are: stage 1 hypertension which is defined as systolic blood pressure (SBP) between 140 . 159mmHg and/or diastolic blood pressure between 90 -99mmHg. Stage 2 hypertension on the other hand refers to all levels of systolic blood pressure greater or equal to 160mmHg and/or diastolic blood pressure greater or equal to 100mmHg. JNC7 also introduced the classification of blood pressure between 120mmHg to 139mmHg systolic blood pressure or 80 to 89mmHg diastolic blood pressure as pre-hypertension, based on the risk of progression and associated cardiovascular risk. Patients with blood pressure in the 130/80mmHg to 139/989 mmHg range have been found to be at twice the risk of developing hypertension, compared with those with lower values (Vasan et al 2000).

1.2 Worldwide Prevalence of Hypertension

The World Health Organisation (WHO) estimated that a quarter of the world's adult population (totalling nearly one billion) had hypertension in 2000. It is predicted to increase to 1.56 billion in 2025, and it has also been suggested that men and women have similar overall prevalence of hypertension worldwide and that such prevalence consistently increases with age in all regions.

Sample national surveys for hypertension conducted in the 1990s (survey sizes ranged from 1800 . 23100) were identified in Germany, Finland, Sweden, England, Spain, Italy, Canada and the United States. The different prevalence, according to country, is: Italy: 37.7%, Sweden: 38.4%, England: 41.7%, Spain: 46.8%, Finland: 48.7%, Germany: 55.3%, United States: 27.8% and Canada: 27.4%. The prevalence of hypertension for the European average was 44.2%, while that for the whole of North America was 27%. (Katharina et al 2003). In these surveys, age-specific hypertension prevalence increased similarly to systolic blood pressure for individual countries, with a higher intercept and slightly higher slope in Europe, compared to Canada and the United States. For example, the prevalence in the age group 35-44 years was 14% in the North American countries and 27% in Europe, and this increased to 53% and 78% respectively, among patients aged 65-74 years.

In cross-sectional surveys of hypertension in four rural and urban communities in sub-Saharan Africa, the age-standardized prevalence of hypertension was 19.3% in rural Nigeria, 21.4% in rural Kenya, 23.7% in urban Tanzania and 38.0% in urban Namibia (Marleen et al 2012).

In a systematic review of 25 studies (> 400 subjects each) from 10 sub-Saharan African Countries namely: Nigeria, Tanzania, South Africa, Ghana, Sudan, Cameroun, Liberia, Eritrea, Senegal and Gambia, prevalence of hypertension ranged from 13 . 48% with rural to urban gradient (Addo et al 2007). The rural, semi-urban and urban prevalence of hypertension in some regions of sub-Saharan Africa are shown in figure 1.2.

1.3 Prevalence of Hypertension in Nigeria

In Nigeria the crude prevalence of hypertension has been documented to be 11.2% (based on blood pressure threshold of 160/95 mmHg) with an age. adjusted rate of 9.3% (Akinkugbe 1997). However, with the current definition of high blood pressure, according to the Seventh Joint National Committee on Prevention, Detection, Evaluation

and Treatment of High Blood Pressure (JNC VII) guidelines, 20 . 25% of adult Nigerians are said to be hypertensive (Ogah 2006). In a meta-analysis of nine community-based studies in Nigeria between 1990 and 2009, the prevalence of hypertension ranged from a minimum of 12.4% to 34.8% and combined prevalence rate was 22%, with 95% confidence interval of 17-27%. In the same meta-analysis, the pooled prevalence of hypertension increased from 8.6% in 1970-1979 to 22.5% in 2000-2011.

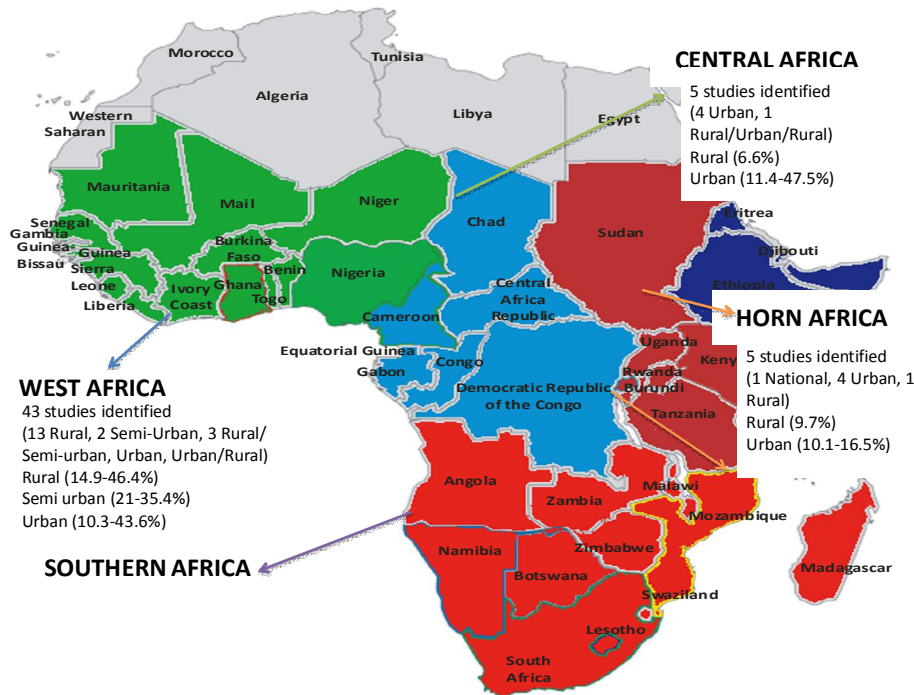


Figure 1.2: Map of Africa Showing Prevalence of Hypertension in some regions

1.4 Hypertension and Target Organ Damage

Hypertension is a major risk factor for cardiovascular disease. It is also a leading cause of cerebrovascular accident, chronic kidney disease and heart failure. (Minino et al 2011). Recent publications have shown that systolic blood pressure (SBP) values are more predictive of cardiovascular disease than diastolic blood pressure values (Benetos et al 2002). It has also been found that each 20mmHg increase in SBP over the range of 115 . 185 mmHg doubles coronary heart disease and stroke mortality (Lewington et al 2002). In addition, hypertension has also been found to be a causal factor in at least 70% of cerebrovascular accident mortality and persons with normal blood pressure have

about half the life time stroke risk of those with hypertension (Bronner et al 1995; Wolf et al 1991).

Furthermore, a relatively small decrease in systolic blood pressure (as low as 10 mmHg) has been shown to be associated with a 25% - 30% lower fatal stroke rate (Staessen et al 2001) and the incidence of end-stage renal disease has been found to increase in parallel with systolic blood pressure. When normal systolic blood pressure of less than 120mmHg is compared with a systolic blood pressure of 140-159mmHg, the relative risk of end. stage renal disease is increased three-fold and for systolic blood pressure of 160 . 179 mmHg, end-stage renal disease risk increases six-fold (Klag et al 1996). In the report of the Prospective TrialistsqGroup, each 20/10mmHg increase in blood pressure doubles the risk of ischaemic heart disease and cerebrovascular accident over the range of 115/75 to 185/115 mmHg in individuals from 40 . 90 years age. The slope of the relationship between hypertension and cerebrovascular disease is about twice as steep as the comparable slope of the cholesterol. CVD relationship (Lewington et al 2002; Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure 1997). One of the main manifestations of hypertension\$ end. organ effects especially in the black population is hypertensive heart disease which is a spectrum of abnormalities that represent the accumulation of structural and functional adaptations to increased blood pressure load. Features of this syndrome include left ventricular hypertrophy, increasing vascular and ventricular stiffness and diastolic dysfunction which ultimately lead to heart failure if not adequately treated (Izzo et al 2004).

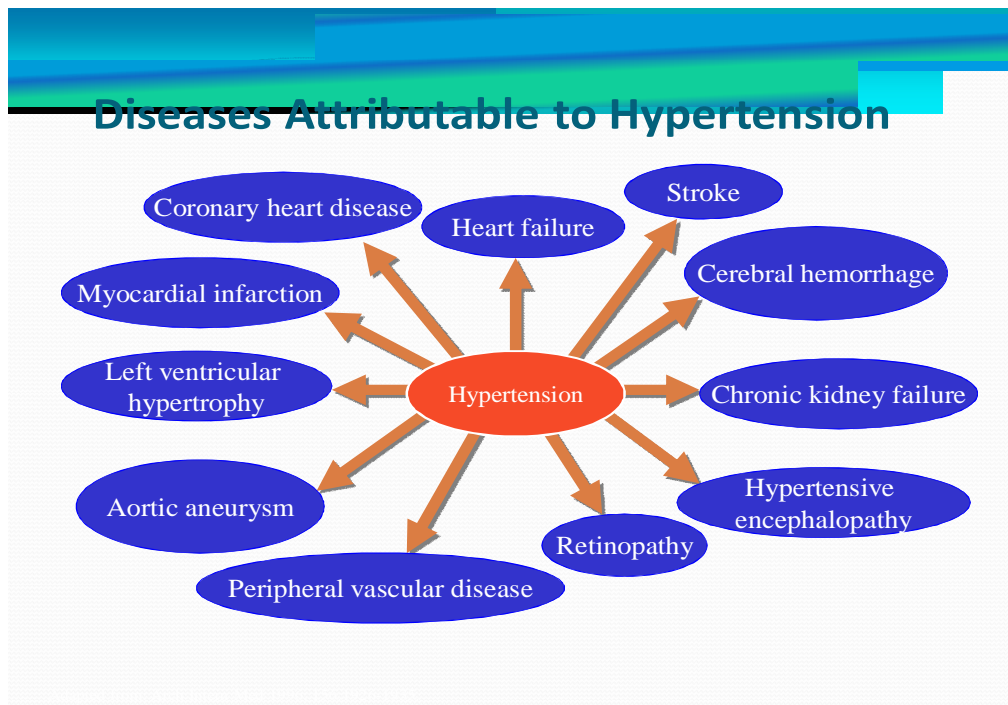


Figure 1.3: Complications of Hypertension (Adapted from Dutsan et al. 1996)

1.5 Hypertension and Left Ventricular Hypertrophy

LVH is defined as left ventricular wall thickness and/or mass and is the best studied marker of hypertensive heart disease (Mensah et al 1994). Increased left ventricular wall thickness and mass have continuously been found to be associated with the level of blood pressure and age. However, without increased systolic blood pressure, clinically significant increases in left ventricular mass do not occur with advancing age. Chronic systolic hypertension therefore seems to be the principal cause of left ventricular hypertrophy (Levy et al 1988; Rheeder et al 1999). LVH serves as an integrated surrogate for cumulated blood pressure load and is best described as being proportional to the area under the lifetime BP curve. This is also supported by the fact that there is a strong association of left ventricular mass and mean 24-hour ambulatory blood pressure (Wendelin. Saarehovi et al 2002; Mancia et al 1997)

Other factors, apart from hypertension and age, that have been linked to left ventricular wall hypertrophy include race (with healthy young blacks having greater left ventricular wall thickness compared to white population), sex, salt intake, insulin and Insulin Growth Factor-I(IGF-I), obesity, high alcoholic intake, plasma viscosity, physical activity and genetics (Akinyemi et al 2009; Hinderliter et al 1992)

Prevalence of Hypertensive Left Ventricular Hypertrophy

In general, echocardiographically determined left ventricular wall hypertrophy ranges from about 20 . 60% in hypertensive individuals. As with other forms of target organ damage, hypertensive left ventricular wall hypertrophy is more prevalent in African-Americans (Post et al 2003). Most studies show higher left ventricular wall thickness in African. Americans than in white hypertensive subjects (Houghton JL et al., 1997; Chaturvedi et al 1984; Gottdiener et al 1994; Gardin et al 1995; Koren et al 1993).

In Ibadan, South-West Nigeria (Aje A et al 2006), LVH was found in 20.8% of the uncontrolled hypertensive group and 24.1% of the controlled hypertensive group when left ventricular mass was indexed to body surface area. However, when left ventricular mass was indexed to height, left ventricular hypertrophy was found in 22.4% of uncontrolled hypertensive subjects and 24.1% of controlled hypertensive subjects. In another study conducted in Ibadan (Salako et al 2009), when 100 newly presenting hypertensives were compared with 100 normal controls, only 28% of the hypertensive subjects had normal left ventricular geometric pattern, compared to 86% of the normal controls.

1.6 Classification of Left Ventricular Hypertrophy

Left ventricular geometric pattern has been classified into four types, based on left ventricular mass index (LVMI) and relative wall thickness (the ratio of wall thickness to cavity diameter). This is shown in figure 1.4: Diagramatic Representation of the Four Left Ventricular Geometric Patterns. Some of these hypertensive patients may develop concentric hypertrophy and others eccentric hypertrophy. Some factors that have been implicated on the geometric pattern developed include the joint influences of volume overload, pressure overload and contractile dysfunction (Ganau et al 1990; Ganau et al 1992; Devereux et al 1994). It has also been shown that some of the apparent variability of the hypertrophic response among hypertensive patients is attributable to the severity, duration or rate of increase of the blood pressure (Ross et al 1997). Patients with concentric versus eccentric hypertrophy have been shown to have higher systolic blood pressures and total peripheral resistance (Ganau et al 1992). In addition, ambulatory blood pressure has been found to be a better correlate of left ventricular mass than single office blood pressure measurements (Fagard et al 1997). For example, subjects with concentric, compared with eccentric hypertrophy, have significantly higher

ambulatory blood pressure, even when the office blood pressure was not dramatically different between the two groups (Devereux et al 1993).

Demographic factors have also been shown to modulate the manner in which the left ventricle responds to an elevation in blood pressure. For example, black subjects compared with whites appear to be predisposed to concentric hypertrophy (Kizer et al 2004; Draznes et al 2005). In subjects with isolated systolic hypertension, women were more likely to develop concentric left ventricular hypertrophy and men more likely to develop eccentric hypertrophy (Krumholz et al 1993). Increasing age has also been associated with concentric, as opposed to eccentric hypertrophy, in hypertensive subjects assessed by echocardiography (Chahal et al 2010)

Combined factors like diabetes, mellitus, obesity and coronary artery disease can also affect the pattern of hypertrophic response. In the Losartan Intervention for End Point Reduction in Hypertension Study, coronary artery disease was associated with an increased left ventricular diastolic dimension and a higher prevalence of eccentric left ventricular hypertrophy (Zabalgoitia et al 2001). Diabetes mellitus has been associated with a concentric hypertrophic response (Palmieri et al 2001). Obesity on the other hand, which is characterised by volume-overload state, is associated predominantly with eccentric hypertrophy (Gottdiener et al 1994; de Simone et al 1994). Another factor which influences the development of either concentric or eccentric hypertrophy in hypertensive subjects is variation in neuro-hormonal activation. For example, differences in plasma rennin activity are widespread in hypertensive subjects. Some investigators have shown that high- versus low- rennin states lead to concentric hypertrophy (Davila et al 2008), while subjects with eccentric hypertrophy have been shown to have low plasma rennin activity (du Cailar et al 2000).

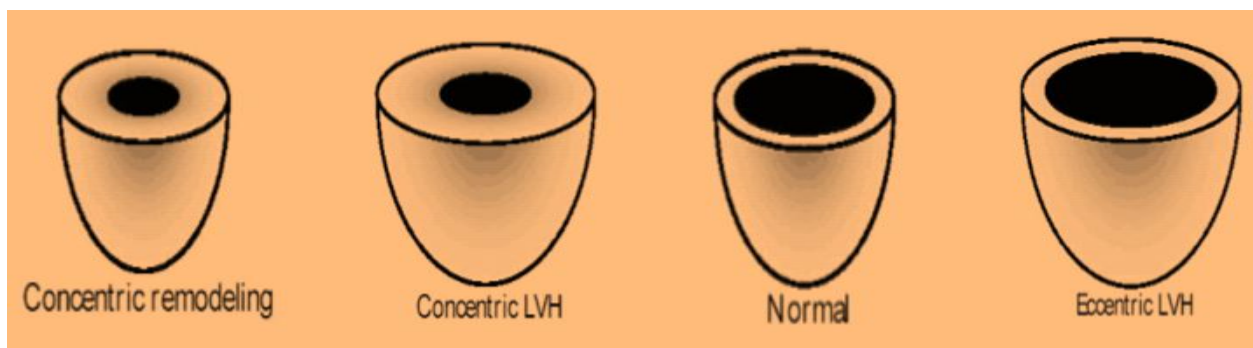


Figure 1.4: Schematic Diagram of the four Geometric Patterns (Adapted from Foppa et al 2005)

1.7 Pathogenesis of Left Ventricular Hypertrophy

Two major triggers for LVH are biomechanical stress and neuro-hormonal factors. LVH is mainly due to pressure or volume overload on the heart. Common causes of pressure overload are systemic hypertension, aortic stenosis, coarctation of the aorta and hypertrophic cardiomyopathy. It is thought that a mechanical signal initiates a cascade of biological events which lead to co-ordinated cardiac growth. There is then an increased myosin heavy chain synthesis (by about 35%) within hours of pressure overload. This increase is initially predicted by an increase in translational efficiency (Imamura et al 1994).

This hypertrophy leads to complex changes in gene reprogramming. These changes include re-expression of immature foetal cardiac genes including: (i) genes that modify motor unit composition and regulation; (ii) genes that encode hormonal pathways, e.g atrial natriuretic factors, and (iii) genes that modify energy metabolism (Swinghedauw et al 1999). Neurohormonal factors that have been implicated in left ventricular hypertrophy include: Angiotensin II, endothelin, calcineurin, metallo proteinases and heterotrimeric G.

Angiotensin II

It has been postulated that angiotensin II, via the AT1 receptor, plays a key role in the induction of hypertrophy because it can directly induce the molecular events of early cardiac growth. Some workers (Sadoshima et al 1993; Harrap et al 1996) in a study of 84 young healthy subjects, aged 16. 24 years, found a direct role for angiotensin II in the development of LVH. Cardiac rennin-angiotensin system has been proposed as an important determinant of hypertrophic response (Dzau et al 1993). The importance of angiotensin II in the development of LVH in hypertensive subjects is also suggested indirectly by the observation that an ACE inhibitor causes regression of left ventricular hypertrophy, more than other antihypertensive drugs (Schmiedert et al 1996).

Endothelin

Some animal studies suggest that endothelin plays a role in the development of left ventricular wall hypertrophy in response to elevated blood pressure (Masaki et al 1991).

Calcineurin

Calcineurin is a calcium calmodulin. dependent phosphatase. It serves as a master switch for clinical hypertrophy. In animal studies, that transgenic mice that over-express components of the calcineurin signalling pathway, develop a hypertrophic phenotype that can be expressed by pharmacological inhibitors of calcineurin (Molkentin et al 1998).

Metalloproteinase (MMPs)

Matrix metalloproteinase is a family of zinc dependant interstitial enzymes. Their tissue inhibitors (TIMPs) control the breakdown of collagen (Woessner et al 1991). The role of MMPs in concentric hypertrophy is not fully understood, but preliminary observations show that they are activated in experimental pressure overload hypertrophy. Studies have also shown that imbalance between MMPs and TIMPs could lead to LVH and diastolic dysfunction (Saglam et al 2006; Ahmed et al 2006).

Heterotrimeric G Proteins

Many hormones and neurotransmitters implicated in the initiation and exacerbation of myocardial hypertrophy including angiotensin II and endothelin, bind to cell membrane receptors which couple to a subset of intracellular heterotrimeric G proteins . the G (q) class (Akhter et al 1998).

1.8 Progression of Hypertension to Hypertensive Heart Failure

This aspect of Cardiovascular Medicine is still highly debated. One theory puts it that the pathogenesis of hypertensive heart failure involves a stepwise progression from hypertension to left ventricular hypertrophy, to heart failure with preserved systolic function and eventually to ventricular dilatation and cardiac failure (Izzo JL et al 2004). An important parallel route to heart failure involves loss of cardiac myofibrils from ischaemic heart disease, which leads directly to segmental wall motion abnormalities and systolic dysfunction (Izzo JL et al 2004). Figure 1.5 shows the possible pathways for the progression of hypertensive LVH to hypertensive heart failure and these include: progression of hypertension to concentric LVH, progression of hypertension directly to hypertensive heart with dilated left ventricle and reduced left ventricular systolic function with or without myocardial infarction, progression of hypertension through concentric hypertrophy to heart failure without or without transient myocardial infarction with reduced left ventricular systolic function and the progression of hypertension through

concentric hypertrophy to heart failure with preserved ejection fraction. In hypertensive subjects in sub-Saharan Africa with the relative low prevalence of coronary artery disease (Damasceno et al 2012), progression of hypertension either directly to heart failure or through concentric LVH without transient myocardial infarction are favoured.

Mechanisms that lead to ventricular dilatation in individuals with decompensating LVH are not completely understood at present (Frohlich ED et al 2003). In patients with systolic dysfunction, activation of the sympathetic nervous and renin-angiotensin-aldosterone systems causes vasoconstriction, salt and water retention and progressive ventricular dilatation and remodelling has been implicated. All the above mentioned processes are maladaptations that create a vicious cycle that worsens cardiac performance (Williams RS et al 1999). As cardiac function declines, there is no further increase in left ventricular mass due to increased apoptosis (Sun Y et al 1998).

In the myocardium the altered gene expression pattern that accompanies the transition from LVH to heart failure includes an overall decrease in contractile proteins (Rerkpattanapipat P et al 2002). At the same time, interstitial protein synthesis continues leading to myocardial stiffness, impaired diastolic relaxation and reduced exercise tolerance (Rerkpattanapipat P et al). Ultimately, there is reduced myofibrillar efficiency, ventricular dilatation and heart failure (Weber KT et al 2001). In addition, concomitant large and small blood vessel changes exacerbate the progression from left ventricular hypertrophy to heart failure. The aorta becomes stiffer with impairment of ventricular-vascular coupling and increased cardiac afterload (Chae CU et al 1999). Coronary flow reserve is also diminished by left ventricular hypertrophy and is eroded further by progressive ventricular dilatation (Cowie MR et al 2002).

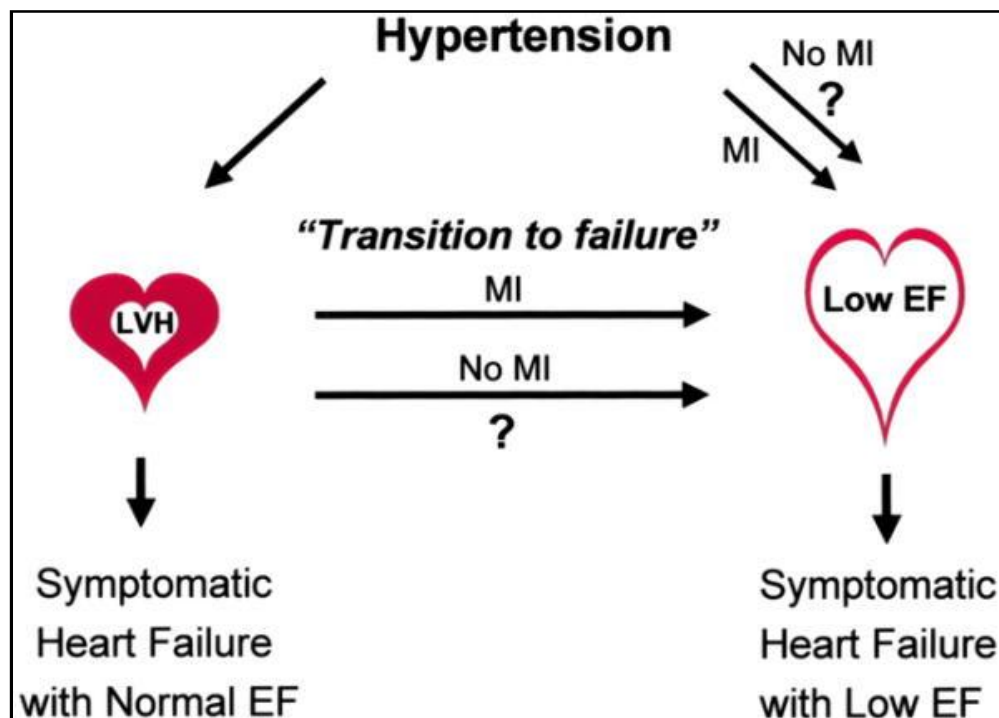


Figure 1.5: The Possible Pathways in the Progression from Hypertension to Heart Failure (adapted from Drazner 2005). MI= Myocardial Infarction, EF= Ejection Fraction

1.9 CLINICAL SIGNIFICANCE OF LVH

Left ventricular wall hypertrophy has been found to be an independent cardiovascular risk factor. It is as potent as systolic blood pressure or age in predicting future cerebrovascular accident, myocardial infarction, sudden death or heart failure (Kannel et al 2003). Bouzas-Mosquera (Bouzas-Mosquera et al 2012) showed in 40138 subjects with echocardiographic determined left ventricular wall hypertrophy, with a mean age of 61.2 years, who were followed up for an average period of 5.7 years, that 9181 subjects died, 901 had nonfatal myocardial infarction and 2139 had nonfatal stroke. Cumulative 10-year mortality was 26.8%, 31.9%, 37.4% and 46.4% in patients with normal, mildly, moderately and severely increased left ventricular mass, respectively ($p < 0.001$). Ten-year rates of nonfatal myocardial infarction and stroke ranged from 3.2% and 6.7% in patients with normal left ventricular mass to 5.3% and 12.7% in those with severe increase in left ventricular mass, respectively. After multivariate adjustment, left ventricular mass remained an independent predictor of all-cause mortality (hazard ratio per 100g increase of 1.21, 95% confidence interval of 1.14. 1. 27 and p -value < 0.001 in women, and hazard ratio of 1.09, 95% CI of 1.04. 1. 13 and p -value < 0.001 in men). For myocardial

infarction hazard ratio was 1.60, with 95% confidence interval of 1.31. 1.94 and p-value <0.001 in women, and for men hazard ratio was 1.15, with 95% confidence interval of 1.02. 1.29 and p-value = 0.019. Lastly, for stroke hazard ratio was 1.26 with 95% confidence interval of 1.13. 1.40 and p-value <0.001 in women, while in men hazard ratio was 1.19 with 95% CI of 1.09. 1.30 and p-value<0.001. They concluded that left ventricular hypertrophy has a graded and independent association with all-cause mortality, myocardial infarction and stroke.

The presence of electrocardiographic. determined LVH (ECG-LVH) has been found to roughly double the risk of subsequent cardiovascular events or death. This is irrespective of race, sex or history of prior coronary artery disease (Vakili et al 2001). Increased ECG voltage in hypertensives also correlates with increased incidence of heart failure episodes (Aronow et al 1998). In echocardiography. based studies, the risk factor. adjusted relative risk of cardiovascular disease was found to be about 50% greater for each increase of 50g/m² in left ventricular mass in men or women (Kannel WB et al). In general, LVH increases cardiovascular disease mortality by about 75% in men and roughly doubles it in women, with a similar impact on all. cause mortality (Levy et al 1998; Levy et al 1989; Levy 1990).

Studies from the Framingham Heart Study have without doubt shown the prognostic value of echocardiographically detected LVH. Echocardiographically detected LVH has been shown to identify a population at high risk for cardiovascular disease (Levy et al 1992). Subjects with left ventricular hypertrophy were found to be older, had higher blood pressure, were more obese and more likely to have pre-existing coronary artery disease and depressed left ventricular systolic function (Levy et al 1990).

Echocardiographic LVH also predicts increased risk of cardiovascular morbidity and mortality, even after adjustment for other major risk factors such as age, systolic and diastolic blood pressure, pulse pressure, treatment for hypertension, smoking, diabetes, obesity, dyslipidaemia, and electrocardiographic evidence of LVH (Haider et al 1998). In apparently healthy subjects followed for a period of 4 years, in whom LVH was defined as left ventricular mass, adjusted for height of 143 g/m in men and 102 g/m in women, the relative risk of developing cardiovascular disease was 1.49 in men and 1.57 in women for each increment of 50 g/m in LV mass. This increment of LV mass was also associated with a relative risk of cardiovascular death of 1.73 in men and 2.12 in women, and a relative risk of all-cause death of 1.49 in men and 2.01 in women. LVH is also associated with an increased risk for sudden cardiac death, which is more

pronounced in men than in women (Krumholtz HM et al 1998). LVH in women is now considered to be a strong cardiovascular risk factor independent of blood pressure (Liao et al 1995, Wassertheil-Smoller et al 2004) and some studies have revealed an increased incidence of atrial fibrillation and sudden death in women with LVH. Patients with hypertensive LVH are at an increased risk of progressing to left ventricular systolic heart failure. Figure 1.6 shows the summary of the effect of LVH on cardiovascular endpoints and Figure 1.7 further illustrates the fact that amongst the four geometric patterns concentric hypertrophy has the least survival.

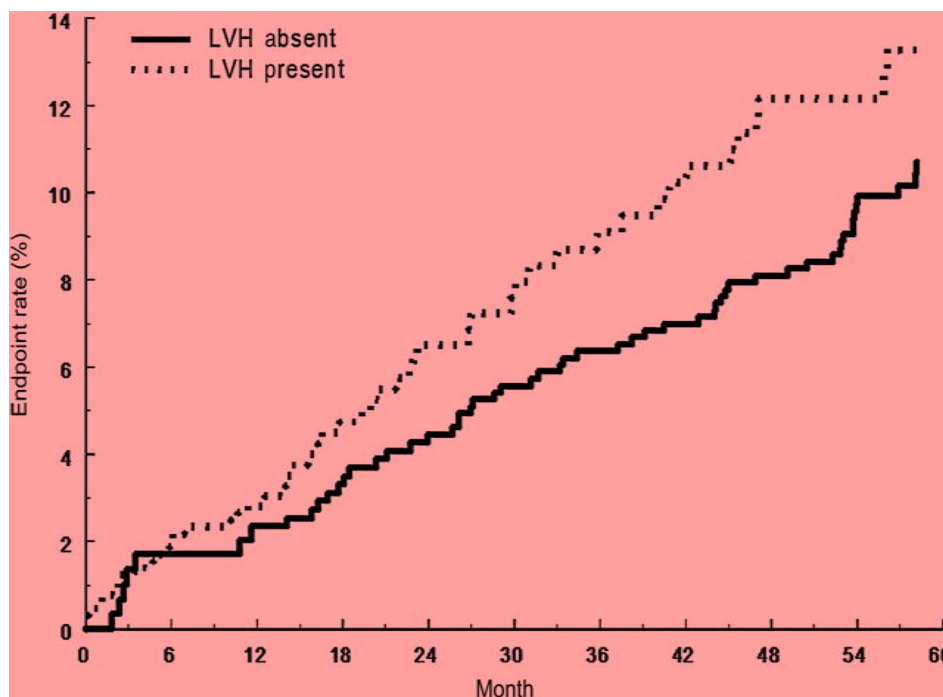


Figure 1.6: Effect of LVH on Cardiovascular Endpoints

Composite endpoint of cardiovascular death, fatal or non-fatal myocardial infarction, and fatal or non-fatal stroke stratified by the time-varying presence of left ventricular hypertrophy (LVH) on echocardiography in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Echo Substudy (adapted from Devereux et al 2004)

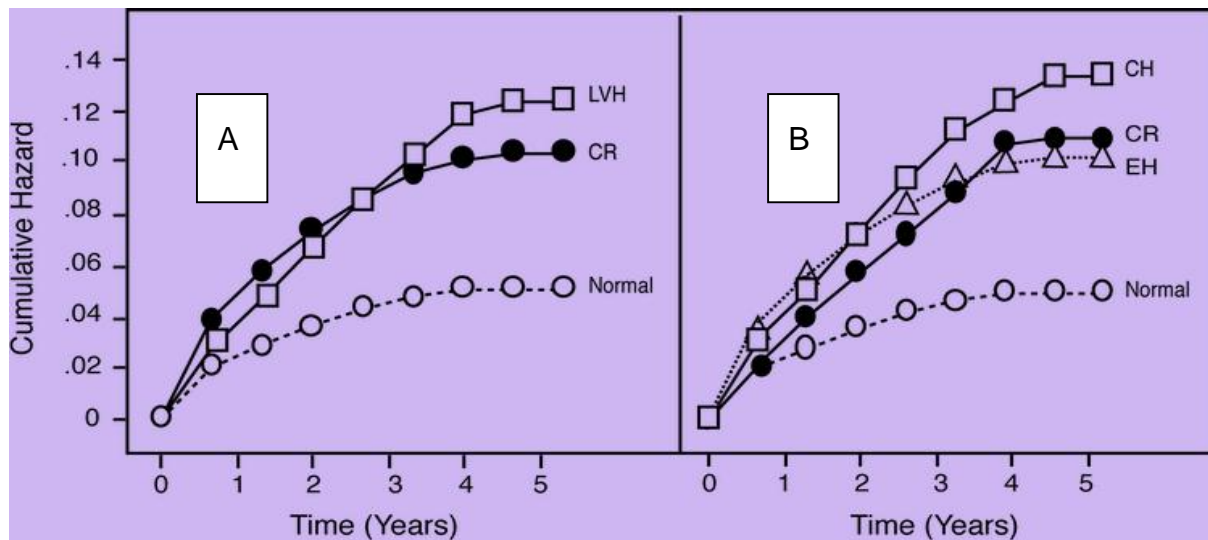


Figure 1.7: Effect of LV Geometry on Survival

Actuarial cumulative hazard plot for survival time based on cardiac structure. A (left), Normal structure, concentric remodelling (CR), and frank left ventricular hypertrophy (LVH). B (right), Normal structure, concentric remodelling (CR), eccentric hypertrophy (adapted from Devereux et al 2004).

1.10 Assessing Left Ventricular Hypertrophy

The most common ways of assessing left ventricular wall hypertrophy is by electrocardiography and transthoracic echocardiography. Electrocardiography is cheap and more widely available, compared to transthoracic echocardiography. However, compared with echocardiography criteria for LVH, electrocardiography has extremely low sensitivity and exhibits limited accuracy (Levy et al 1990).

In a review of the role of electrocardiography in detecting LVH with strain pattern, the prevalence of electrocardiographic strain pattern ranged from 2% to 36% with the highest prevalence occurring in the era before good antihypertensive therapy. The sensitivity as a measure of LVH ranged from 2% to 36% (Ogah et al 2006). Electrocardiography has also been found to have low sensitivity for detecting magnetic resonance imaging defined LVH (Jain A et al 2010).

An example of the limitation of electrocardiography is seen in the Heart of Soweto Study in which 387 electrocardiographic recordings subjects, found to be heart disease free on echocardiography, showed that 51% had an ECG abnormality+ or normal variant and 67 ECGs (17%) had major and minor abnormalities (Sliwa et al 2012). The Sokolow Lyon

Index voltage exceeding 38mm, indicative LVH, were found to be more prominent in males than females(23.6% vs.6.4%; OR=4.5; 95% CI 2.3-8.5) (Sliwa et al 2012).

In another study of 334 Africans, the performance of classic electrocardiographic criteria for the detection of LVH was largely disparate and appeared to be lower than in Caucasians (Jaggy et al 2000).

Pathological left ventricular wall hypertrophy may be associated with non-existence of symptoms for many years before the development of complications such as congestive heart failure or unexpected sudden death. Therefore, in contemporary clinical practice and population studies, the diagnosis of LVH depends predominantly on echocardiographic measurements or novel non-invasive imaging techniques. Two-dimensional targeted M-mode echocardiographic measurements of LV dimensions and the calculation of LV mass are now standardized (Vuille et al 1994). The detection of pathological LVH requires adjustments for sex, height, and body mass. Even though multiple studies have offered echocardiographic criteria for LVH, the analyses of the large original cohort and offspring subjects of 56148 of the Framingham Heart Study have provided criteria that are based on a healthy population distribution of LV mass (Levy et al 1987). Using these mass/height criteria, the prevalence of LVH in the entire Framingham Study population was 16% in women and 19% in men. Echocardiographic LVH is also more prevalent than LVH detected by electrocardiography, with overall rates of 17.4% versus 2.4%, respectively (Levy

et al 1987). Normal ranges of LV and right ventricular mass have been described in healthy male and female subjects using cine-MRI, as well as ultrafast CT. In a recent study of 75 healthy subjects, the upper limit (95% confidence limit) of LV mass normalized to body surface area was 113 g/m² in men and 95 g/m² in women (Lorenz et al 1999). The review by Lorenz et al (Lorenz et al 1999) summarizes normative sex-based values of LV mass reported by additional contemporary MRI and CT studies. In comparison with the Framingham Heart Study, which used echocardiographically detected LVH, current novel imaging studies are limited by the much smaller size of the study populations and less robust longitudinal outcome data.

Although, the awareness and availability of echocardiography in sub-Saharan Africa is increasing, it is still not widely accessible because of high cost (Reichek et al 1981; Adamu et al 2001). Transthoracic echocardiography results may also not be adequate in all patients, especially in those with obesity and pulmonary disease (Levy et al 1990; Devereux et al 1984). With the limitations of electrocardiography and echocardiography,

especially in sub-Saharan Africa, there is the need for cardiovascular scientists to turn to biochemical markers such as NT-Pro BNP, BNP and other novel biomarkers which can be used to evaluate various spectrum of hypertension, hypertensive heart disease and hypertensive heart failure (Buckley et al 1998).

1.11 Hypertensive Heart Failure

Heart failure is a very dominant health issue in developed societies and the most common cause of hospital admission for patients over the age of 65 years. It is also the single most important consumer of healthcare dollars (Vasilios et al 2001). In some European countries and the United States, as much as 1% of the health budget is spent on the management of heart failure. In the United States in-patient treatment of heart failure accounts for about thirteen billion US dollars per year and the amount spent on outpatient management is at least four times higher.

With improvements in the control of communicable diseases, malnutrition and rapid urbanisation, cardiovascular diseases such as hypertension and cerebrovascular accident are increasingly recognised as significant causes of morbidity and mortality in most African countries (Muna et al 1993). Nowadays, cardiovascular diseases account for 7 . 10% of all medical admissions to hospital, with heart failure contributing 3 . 7% (Onwuchekwa et al 2009).

Hypertension is the most common cause of heart failure and most patients who develop heart failure have a history of hypertension (Vasilios et al 2004). In the Global Burden of Disease 2010 Project (Murray CJL et al 2010), hypertensive heart disease which comprises hypertension, hypertension with LVH and hypertensive heart failure, was ranked one of the most common causes of disability adjusted life years. In a study by Perera before the availability of effective anti-hypertensive drug therapy, of the 500 patients with uncontrolled hypertension followed for over 20 years, 50% died of heart failure (Perera et al 1995). In the Framingham Heart Study, hypertension accounted for 39% of heart failure in men and 59% in women (Levy et al 1989; Levy et al 1990; Vasan et al 1990).

In a recent survey of the causes, treatment and outcome of acute heart failure in 1006 Africans from nine sub-Saharan Africa countries, heart failure was most commonly due to hypertension in 453 subjects (45.4%) (Damasceno A et al 2012). In the sub-Saharan

African population, hypertension is the leading cause of heart failure in Nigerians accounting for about 60% (Ojji et al 2009; Onwuchekwa et al 2009). Hypertension is also the leading cause of heart failure in Cameroon, accounting for about 54% of all heart failure cases (Kinque et al 2005). In 1960 cases of heart failure studied in the Heart of Soweto study, hypertensive heart failure accounted for the highest form of heart failure in 281 (33%) of the study cohort (Stewart S et al 2008).

In a recent publication of the Abuja Heart Study (Ojji et al 2013), in a cohort of 1,515 subjects attending a cardiac clinic in a tertiary set up, hypertensive heart failure was the commonest form of heart failure in 60% of cases and accounted for 33% of the total cohort.

1.12. BNP and NT-Pro BNP in Hypertensive Heart Disease

BNP and NT-pro BNP

BNP consists of 32 amino-acids with a central ring of 17 amino-acids created by a disulphide bond between cystine bases (Cowie et al 2002). *Figure 2: Structure of Pro BNP and NT-pro BNP.* BNP is secreted by myocardial cells located on both atria and ventricles, mainly by left ventricular myocardial cells. BNP gene is located on the short arm of chromosome 1, close to the ANP loci. Its mRNA is translated to a chain of 108 amino acids called pro BNP that co-exist with ANP in some secretory vesicles of the atrial and ventricular myocardial cells. Pro BNP is transformed to BNP and to NT-pro BNP, an endocrinologically inactive molecule (Bolger et al 2002; Kroger 2002).

BNP and NT-pro BNP in Assessing Hypertensive Heart Disease

Left ventricular hypertrophy has been reported as one of the conditions in which plasma BNP and NT-pro BNP significantly exceed the normal range (Takeda et al 1995). Plasma BNP level has been found to be a useful marker of left ventricular hypertrophy in hypertension and has been found to rise progressively with increasing severity of hypertension, particularly when ventricular hypertrophy is present. Similarly, it has been shown by some other workers (Santiago et al 2009) that plasma BNP and NT-pro BNP levels are useful to discriminate between patients with regard to cardiac remodelling, and they suggested that they should be considered as a screening tool in order to select hypertensive patients eligible for transthoracic echocardiography. Furthermore, in a

more recent study, NT-pro BNP has been found as an independent predictor of survival in patients with hypertension and increased left ventricular mass (Santiago et al 2009).

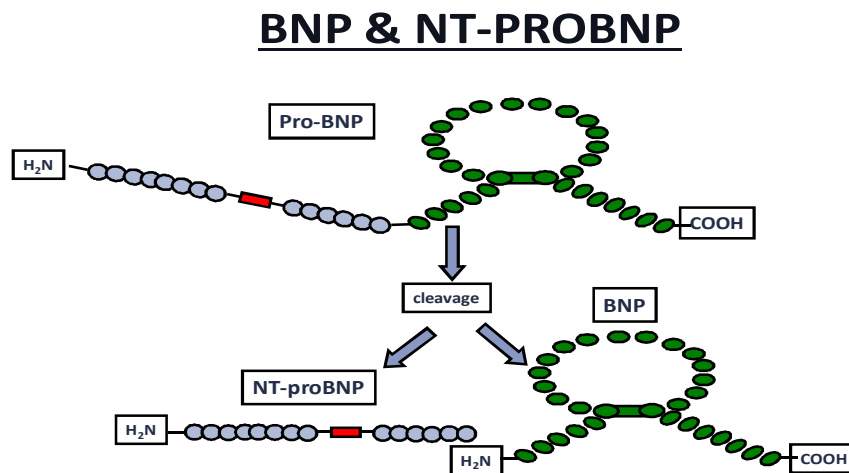


Figure 1.8: Structure of BNP and NT-PRO BNP

Plasma BNP and NT- pro BNP in Heart Failure

The usefulness of BNP in heart failure can be divided into three, which include making of diagnosis, prognostication of disease conditions and assessment of therapy.

Making Diagnosis

Its usefulness in diagnosis covers conditions such as left ventricular diastolic dysfunction, left ventricular systolic dysfunction after acute myocardial infarction and right ventricular heart failure. It has been proposed that patients with BNP concentrations of less than 20pmol/L have less chances of suffering from heart failure, while patients with higher concentrations should have further cardiovascular investigations (Talwar et al 2000, Hunt et al 1997). Recent studies in patients with normal systolic function verified by echocardiography have shown that BNP levels correlate well with Doppler measurements showing diastolic dysfunction of the left ventricle (Moser et al 2002). Theoretically, NT- pro BNP is said to be better in identifying patients with heart failure. Its increase is also said to be greater than that of BNP and its plasma concentration more stable (Kohno et al 1992; Nishigaki 1996).

Prognostication of Disease Conditions Using BNP and NT-Pro BNP

Published studies indicate that that BNP or NT-pro BNP plasma concentration provides important information on the prognosis of heart failure and support its use as an adjuvant to clinical assessment especially in centres where risk stratification is of great importance, for example in transplantation units (Hasegawa et al 1993). **In eight randomized controlled trials with a total of 1726 patients with a mean duration of 16 months, B-type natriuretic peptide-guided therapy was found to reduce all-cause mortality in patients with chronic heart failure compared with usual clinical care especially in patients younger than 75 years (Parapakkham et al 2010).**

Assessment of Therapy

It has also been found out that assessing BNP levels and adjusting the dosage of therapy according to its level can lead to achieving the best possible treatment of heart failure (Cowie et al 2002). It has been shown by these workers that BNP concentration of less than 100pg/ml correlates with functional improvements in patients with heart failure and also linked to decreased clinical endpoints, such as cardiovascular death. They further suggested that using BNP concentrations to monitor patients with heart failure and managing their medical therapy accordingly might improve overall morbidity and mortality.

Choosing NT-pro BNP ahead of BNP

Measuring NT-pro BNP has significant advantages over routine BNP, even though the levels of the two will be the same under ideal circumstances. NT-pro BNP is more stable than BNP with a half-life of 60-120 minutes, as against a half-life of 18-22 minutes for BNP. Once blood is collected BNP levels are not stable in vitro for long periods, dropping significantly over the first 24 hours, while there is very little variation in the level of NT-pro BNP for at least 72 hours or even longer. Therefore, NT-pro BNP can be assayed from stored or delayed specimens with confidence that the levels have not degraded with storage. In addition, assaying NT-pro BNP has been found to be easier

than assaying BNP and this is because of higher plasma concentration. NT-pro BNP has also been found to be better in identifying patients with heart failure. Its increase in heart failure has also been found to be greater than that of BNP and its plasma concentration is more stable (Kohno et al 1992; Nishigaki et al 1996)

1.13 Novel Biomarkers of Hypertension, Hypertensive Heart Disease and Hypertensive Heart Failure

In the last few years, the identification of biomarkers of potential usefulness for the clinical handling of hypertension evolving to hypertensive heart disease and hypertensive heart failure has been a prolific field (Arantxa et al 2009). The rapid acceleration of the investigation of novel circulating biochemical markers of myocardial remodelling in hypertensive heart disease has also caused the clinical and research communities to be faced with candidate molecules of which very few are likely to survive the test of time as useful clinical tools (Vasan et al 2006; Morrow et al 2007).

A number of the biochemical markers that have been studied include Cardiotrophin-1, Annexin A5, Carboxy-terminal pro-peptide of procollagen type 1 and Matrix metalloproteinase-1. Cardiotrophin-1 appears to be the most promising of these markers as regards the criteria for the ideal biochemical marker (Arantxa et al 2009).

Cardiotrophin-1 is a cytokine member of the interleukin-6 super family which is produced by cardiomyocyte and cardiac fibroblasts in situations of biochemical stress and under exposure to humoral factors such as angiotensin II (Kuwahara et al 1991; Sano et al 2000). Once it is secreted it interacts with its receptor, which is a heterodimer formed by glycoprotein 130 and the leukaemia inhibitory factor receptor activating different signalling pathways thereby leading to cardiomyocyte growth dysfunction (Pennica et al 1996).

Plasma cardiotrophin-1 concentration has been found to be increased in hypertensive patients as a whole group, compared to normotensive subjects (Lopez et al 2006; Pemberton et al 2005). It has also been reported that plasma cardiotrophin-1 is higher in patients with LVH than in patients without LVH (Lopez et al 2005), and in patients with heart failure than in patients with LVH (Asal et al 2000). In addition, it has been found out that 31% of hypertensive patients without LVH already exhibited concentrations of cardiotrophin-1 abnormally elevated above the upper normal limit measured in the

normotensive control population which suggests that cardiotrophin-1 increases early in the evolution of arterial hypertension (Gonzalez et al 2007).

An association exists between anti-hypertensive-induced decrease of plasma cardiotrophin-1 and reduction of left ventricular mass index in patients with left ventricular hypertrophy (Gonzalez et al 2005). Abnormally high plasma cardiotrophin-1 concentration is associated with reduced fractional shortening and altered relaxation in patients with inappropriate left ventricular mass (Lopez et al 2007).

Lastly, cardiotrophin-1 presents an acceptable sensitivity of 70% and specificity of 75% to detect LVH, as assessed by echocardiography in hypertensive patients (Lopez et al 2007).

Soluble ST2 as a Novel Biomarker

The most recent novel biomarker is soluble ST2. The ST2 receptor is a member of the Toll-like/interleukin-1 (IL-1) receptor family. A large amount of research work in animal models have shown that cytokine IL-33 interacts with ST2 receptors in cardiac myocytes, thereby comprising a cardio protective stress-responsive signaling system (Kakkar et al.2008; Sanada et al 2007). ST2 exists in two forms - transmembrane and soluble forms. Soluble ST2 is a candidate of biomarker in cardiovascular disease. It was shown that mice treated with exogenous IL-33 demonstrate reduced hypertrophy and transgenic deletion of ST2 abolishes this salutary effect, thereby resulting in severe myocardial hypertrophy and fibrosis (Sanada et al 2007). Figure 3 shows the structure of ST2.

In response to inflammation and cardiac stress, IL-33/ST-2 signaling becomes activated and the soluble form of ST2 is released into the circulation (figure 1.6). The soluble form of ST2 acts as a decoy receptor, sequestering and inhibiting IL-33 and this potentially explains why we, and others, have observed that higher circulating levels reflect increased cardiac risk (Kakkar et al 2008). Genomic technology has been used to identify ST2 as a gene markedly induced in mechanically overloaded cardiac myocytes (Weinberg et al 2002; Weinberg et al 2003).

The above point further suggests that ST2 is induced in conditions of myocardial overload, such as myocardial infarction, when the remaining viable myocardium must bear more stress. Soluble ST2 have been found to be increased in the serum of patients one day after myocardial infarction. In addition, serum ST2 levels predict outcome in

patients with heart failure and a change in ST2, over time, is also associated with prognosis.

Although the lung has been shown to have the highest expression of soluble ST2 levels (Mildner et al 2010), potential cellular sources of soluble ST2 in the cardiovascular system include endothelial cells (Bartunek et al 2008; Aoki et al 2010) and cardiac myocytes (Mildner et al 2010).

The first study to demonstrate that serum soluble ST2 level was elevated early after acute myocardial infarction was carried out in sixty nine human samples and showed that soluble ST2 levels correlated with creatinine kinase and correlated inversely with left ventricular ejection fraction (Weinberg et al 2002). Two larger studies have since demonstrated the prognostic value of measuring serum soluble ST2 in acute myocardial infarction. Shimpō et al (Shimpō et al 2004) measured serum soluble ST2 in eight hundred and ten (810) patients with acute myocardial infarction (AMI) in the Thrombolysis In Myocardial Infarction (TIMI)-14 and Enoxaparin and TNK-tPA with or without Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor as Reperfusion Strategy in STEMI(ENTIRE)-TIMI-23 clinical trials. They demonstrated in these two studies that baseline levels of soluble ST2 were higher in patients who died or developed congestive heart failure.

Soluble ST 2 levels were also measured in 1239 patients from the Clopidogrel as Adjunctive Reperfusion Therapy=Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial (Sabine et al 2008). The authors found that high levels of soluble ST2 at baseline were a significant predictor of cardiovascular mortality and heart failure and combined measurement of ST2 and NT-pro BNP significantly improved prediction of cardiovascular death. Measurement of soluble ST2 early after acute myocardial infarction in one hundred patients undergoing cardiac Magnetic Resonance Imaging also assisted in the prediction of adverse left ventricular functional recovery and remodelling (Weir et al 2010). In an outpatient study, soluble ST2 levels also reflected right-side heart size and function, and these were an independent predictor of one-year mortality in outpatients referred for echocardiography (Daniels et al 2010).

Several other studies have obtained similar findings that soluble ST2 levels correlate with severity of heart failure, left ventricular ejection fraction, creatinine clearance, B-type natriuretic peptide, C-reactive protein and are a predictor of mortality (Boisot et al 2008; Mueller et al 2008; Pascual-Figal et al 2009; Bayes-Genis et al 2010). Concentrations of soluble ST2 have also been found to be predictive of mortality in dyspnoea patients with

and without acute destabilized heart failure (Januzzi et al 2007; Martinez-Rumayor et al 2008; Mueller et al 2008; Januzzi et al 2008; Shah et al 2009; Dieplinger et al.,2010).

In addition, cardiac surgery patients undergoing coronary artery bypass grafting with cardiopulmonary bypass demonstrate a significant rise in soluble ST2 levels twenty four hours after surgery (Szerafin et al 2005; Szerafin et al 2009). Putting all these things together, these studies indicate soluble ST2 has the potential to be a predictive cardiovascular biomarker in patients with acute myocardial infarction, heart failure and dyspnoea.

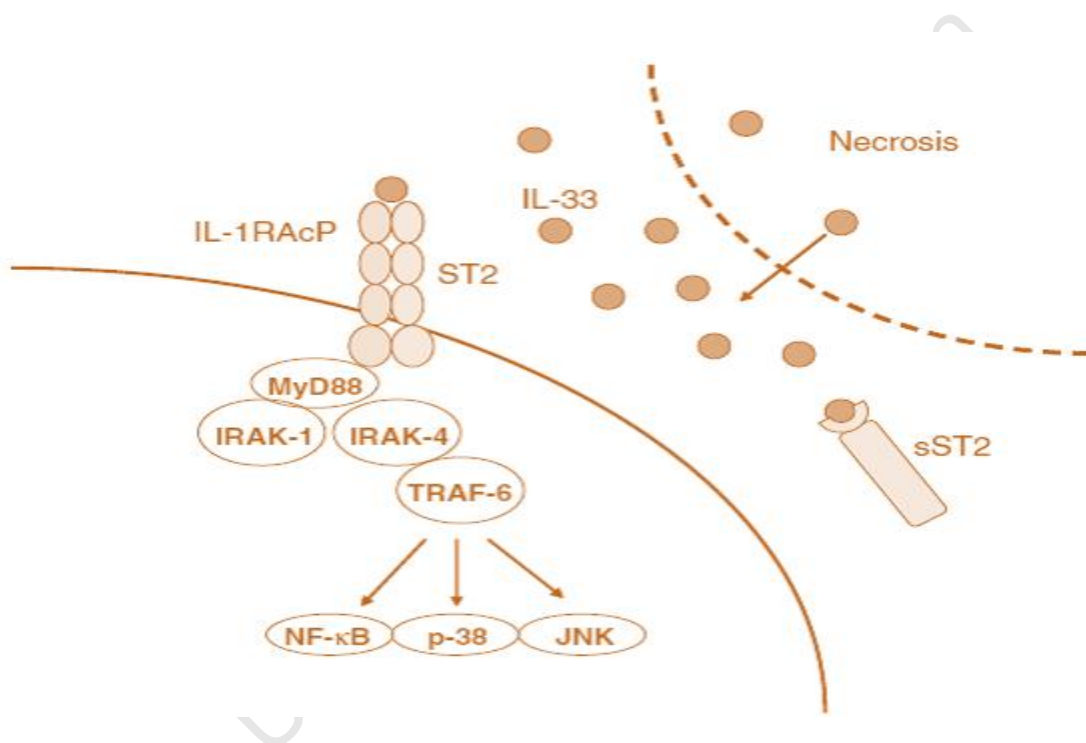


Figure 1.9: The structure of ST2 and Activation of ST2 Receptor (adapted from Miller Am et al 2011).IL-33 that is secreted by necrotic cells can activate the heterodimer ST2/IL-1RAcP receptor complex leading to the recruitment of MyD88 and IRAK 1 and 4, and activation of two other pathways as shown above.

1.14 Problem Statement and Rationale

In black Africans, primary hypertension is the most common cardiovascular risk factor (Ajayi et al 1993), with a higher age-adjusted prevalence compared to Caucasians

(Seedat et al 2000). In a recent systematic review of 25 studies from 10 sub-Saharan African countries, prevalence of hypertension ranged from 13 . 48% with rural to urban gradient (Addo J et al 2007).

Common complications of hypertension in black Africans, apart from cerebrovascular accident and chronic kidney disease, are LVH and heart failure. Since the burden of hypertensive heart disease is enormous in black Africa, there is the need to look for easier and faster bedside means to differentiate between the various spectrums of hypertensive heart disease, as this affects the prognosis, management and treatment modalities in hypertension.

Hypertensive Heart Disease: A big burden-the need for point-of-care screening

There is a need to differentiate the various spectrum of hypertensive heart disease early as this will determine the various therapeutic approaches, such as the initiation of agents such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-1-selective agents. A biomarker which can be used as point-of-care by the bedside will be necessary. Although more conventional electrocardiography and echocardiography are the diagnostic tools in this regard, electrocardiographic criteria are insensitive, while echocardiography is not so easily accessible, uneconomical and may not be adequate in all patients, especially in those with obesity or pulmonary disease. In most parts of sub-Saharan Africa people either have to travel long distances or wait for a very long period of more than four months to have transthoracic echocardiography performed.

Early detection of concentric hypertrophy amongst left ventricular hypertrophy

LVH is classified according to geometric pattern into four types, which are concentric hypertrophy, eccentric hypertrophy, concentric remodelling and normal geometry (Ganau et al 1992). Patients with concentric LVH have a higher prevalence of associated cardiovascular complications or death than those with other geometric patterns. This is illustrated in figure 2.0 which shows the mortality in four geometric patterns, in 9771 elderly patients, and is further illustrated in figure 2.1, which also shows mortality in four left ventricular geometric patterns in 11792 obese patients with preserved ejection fraction. These figures highlight that concentric hypertrophy have significantly higher mortality compared to other geometric patterns. Patients with

concentric hypertrophy also have the most advanced extra-cardiac target-organ damage, compared with other groups (Koren et al 1991) and, therefore, there is the need for early diagnosis and instituting of therapy with medications, including the rennin-angiotensin-aldosterone blockers for patients with LVH, especially concentric hypertrophy. Since echocardiography is not easily accessible, especially in resource poor settings, and there may be problems of interpretation in those with obesity or pulmonary disease, there is therefore the need for cardiovascular scientists to look for easier and more accurate methods, especially at the bedside, of assessing the cardiac structural changes in hypertension. One biomarker that has been found to be a marker of left ventricular remodelling in hypertension in Caucasians is BNP (brain natriuretic peptide) and NT- pro BNP. Another biomarker that has been found by cardiovascular scientists as a biomarker for cardiovascular diseases is soluble ST2, which is a member of the interleukin-1 receptor host defence and inflammation family.

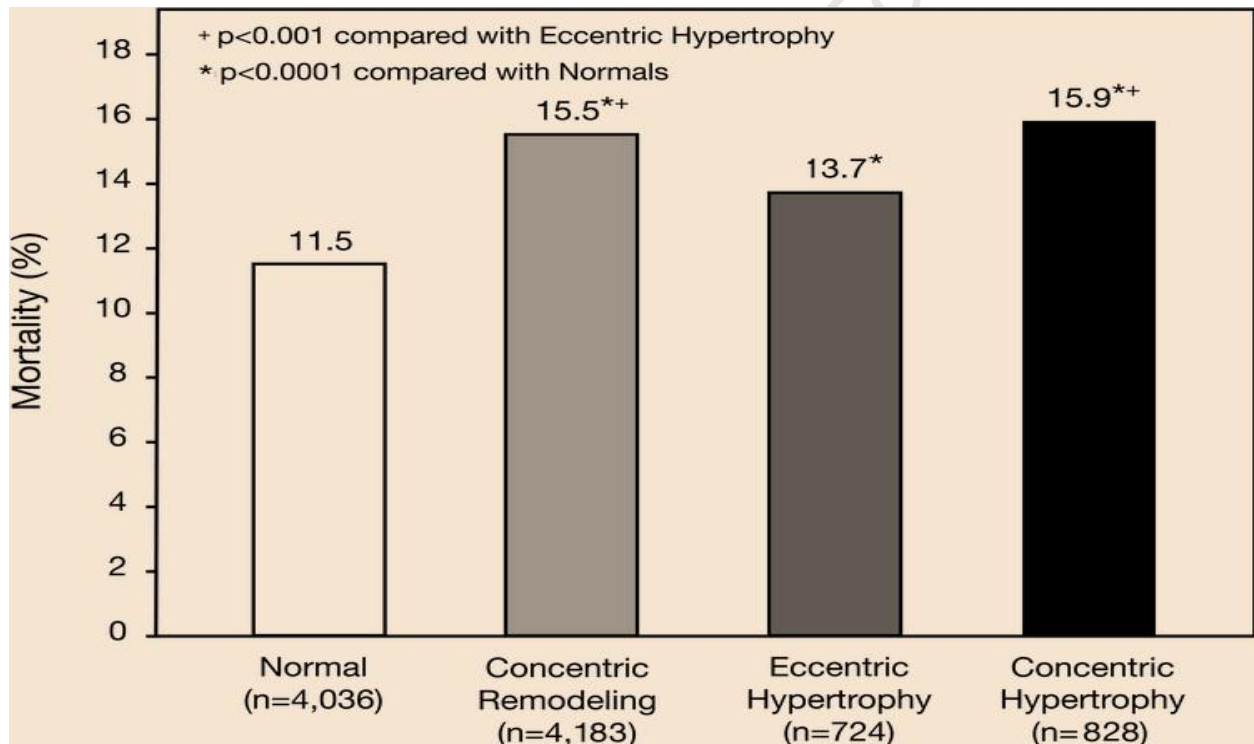


Figure 2.0: Mortality in 4 left ventricular geometric patterns in 9771 elderly patients aged more than 70 years with normal ejection fractions (adapted from Lavie et al 2006).

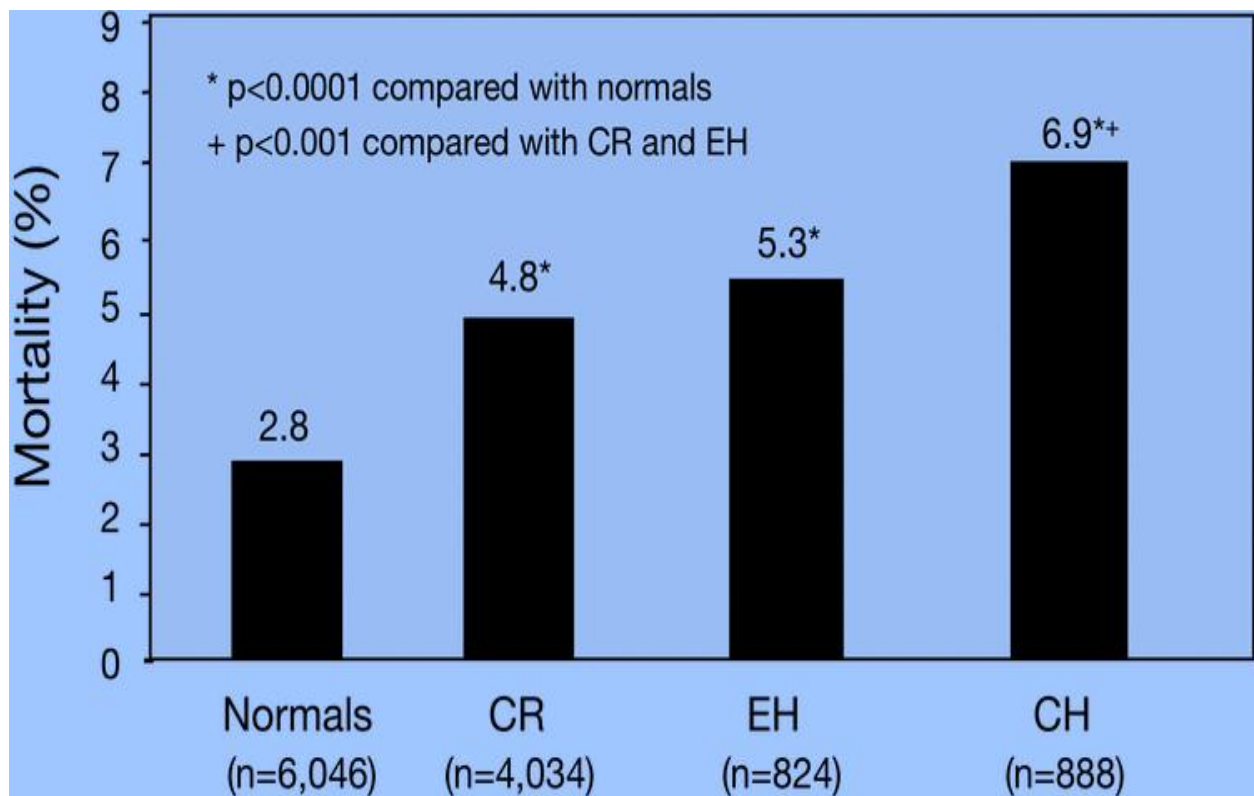


Figure 2.1: Mortality in 4 left ventricular geometric patterns in 11 792 obese patients with preserved ejection fraction (Milani et al 2006). CR=Concentric remodelling, EH=Eccentric Hypertrophy, CH=Concentric Hypertrophy.

NT-pro BNP as a valid Biomarker in Hypertensive Heart Disease in sub-Saharan Africa

Plasma BNP and NT-pro BNP levels have been found to be a marker of left ventricular hypertrophy in hypertension and has also been found to rise progressively with increasing severity of hypertension, particularly when ventricular hypertrophy is present. Similarly, it has been shown by some other workers (Buckley 1993) that plasma BNP and NT-pro BNP levels differentiate patients with regard to cardiac remodelling and they have suggested that they should be considered as a screening tool in order to select hypertensive patients eligible for transthoracic echocardiography. In addition, NT-pro BNP has been shown to be a biomarker that differentiates hypertensive subjects with left ventricular wall hypertrophy from those with heart failure (Santiago et al 2009, Talwar et al 2000). Most of the current knowledge and published data on plasma NT- pro BNP as a marker in hypertensive left ventricular hypertrophy and hypertensive heart failure are based on studies in Europe and the United States of America, with a dearth of data in Africans, where the burden of hypertension and hypertensive disease is very high (Stewart et al 2011; Ojji et al 2013). For example, the THESUS study, which studied 1006 acute heart failure subjects in nine sub-Saharan African countries inclusive of

Nigeria, showed that hypertension was the most common cause of heart failure, accounting for heart failure in 45.4% of cases (Damasceno et al 2012). In addition, most previous studies on this subject never considered left ventricular diastolic function or right ventricular function, both which have been found to be prognostic markers in hypertensive heart disease (Myslinski et al 1998; Giuseppe et al 2002). We therefore proposed to examine the effect of NT- pro BNP on left and right ventricular remodelling in an African Hypertensive cohort.

ST2 as a Possible Biomarker in Hypertensive Heart Disease

Soluble ST2 is a member of the interleukin-1 receptor host defence and inflammation family (O'Neil et al 2000, Shimpo et al 2004). Soluble ST2 is induced in conditions of myocardial overload, such as acute myocardial infarction, when the remaining viable myocardium must bear more mechanical stress (Shimpo et al 2004, Townsend MJ et al 2000) and has also been recently reported to be increased in hypertension (Coglianese et al 2012). In spite of the use of serum soluble ST2 as a marker in the field of cardiovascular medicine, there is a global dearth of data on the role of soluble ST2 in hypertensive heart disease. We therefore proposed to study the role of soluble ST2 in differentiating the various spectrum of hypertensive heart disease, with the ultimate goal of developing a point of care for early and easy differentiation of the various spectrum of hypertensive heart disease.

Chapter 2

2.0 Aims, Hypothesis and Objectives

2.1 Background

Although hypertension affects every ethnic group, the consequences are said to be more devastating among blacks. One of the main manifestations of hypertension's end-organ effects especially in blacks is hypertensive heart disease which includes LVH, increasing vascular and ventricular stiffness and diastolic dysfunction which ultimately lead to heart failure (HF) if not adequately treated.

In spite of the high burden of hypertension, hypertensive left ventricular wall hypertrophy and hypertensive heart failure and the limitations of electrocardiography and transthoracic echocardiography as diagnostic tools in these conditions, there is a paucity of data in the sub-Saharan African population on the use of both conventional and novel biomarkers as screening and diagnostic tools in hypertension, hypertensive left ventricular hypertrophy and hypertensive heart failure.

The aim of this study was therefore to explore the role of conventional biomarker NT-pro BNP and the novel biomarker ST2 in differentiating the various spectrum of hypertension-hypertensive heart disease with the ultimate goal of developing point of care tests to complement the more conventional electrocardiography and echocardiography.

2.2 Hypothesis and Objectives

We hypothesise that the biomarker NT-pro BNP can differentiate a hypertensive cohort with/without left ventricular hypertrophy from hypertensive patients with heart failure, but will not be sensitive enough to differentiate hypertensive subjects with left ventricular hypertrophy from patients without left ventricular hypertrophy. We also hypothesise that the novel biomarker ST2 is a more sensitive biomarker than NT-pro BNP in differentiating the various spectra of hypertension-hypertensive heart disease.

2.3 What are the aims of this study?

To fulfill the aims of the present study the following objectives as shown in figure 2.1 were pursued:

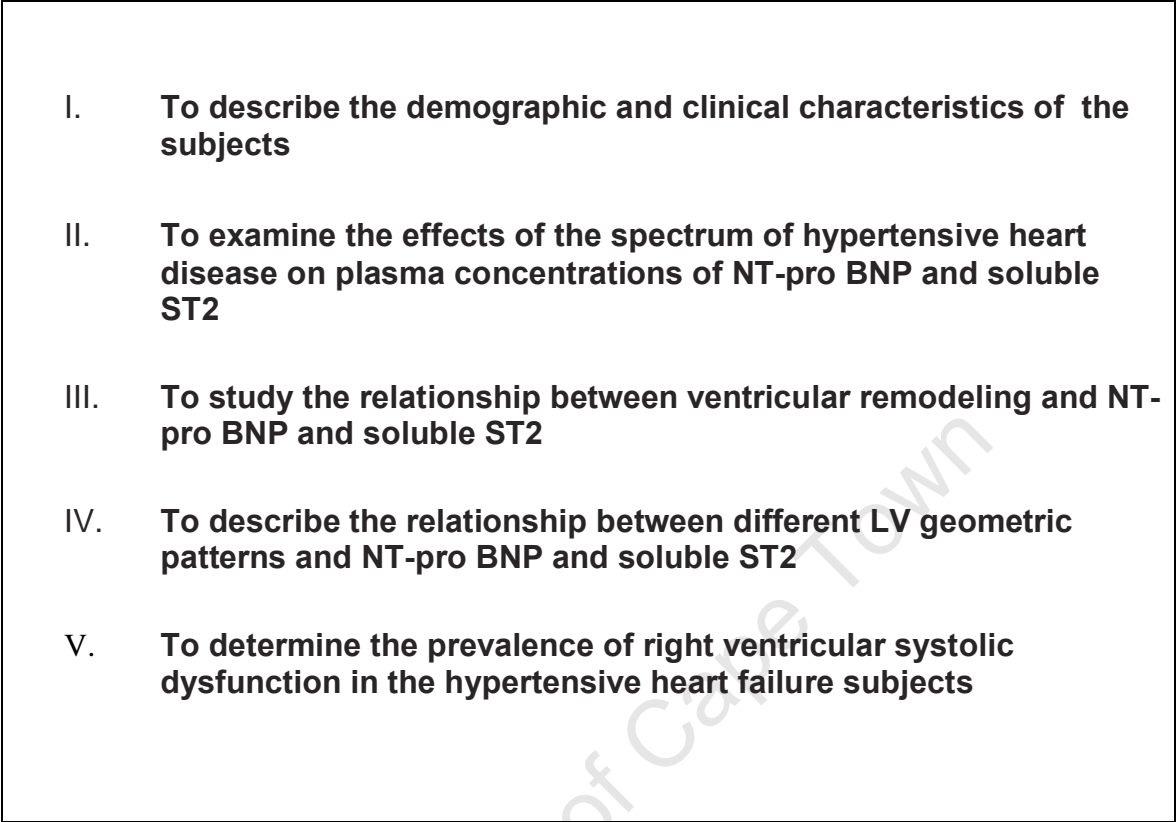
- 
- I. **To describe the demographic and clinical characteristics of the subjects**
 - II. **To examine the effects of the spectrum of hypertensive heart disease on plasma concentrations of NT-pro BNP and soluble ST2**
 - III. **To study the relationship between ventricular remodeling and NT-pro BNP and soluble ST2**
 - IV. **To describe the relationship between different LV geometric patterns and NT-pro BNP and soluble ST2**
 - V. **To determine the prevalence of right ventricular systolic dysfunction in the hypertensive heart failure subjects**

Figure 2.1: Aims of the study

CHAPTER 3

3.0 METHODS

3.1 Study Group

This is a prospective cohort study. The study was approved by the University of Abuja Teaching Hospital Ethical Clearance Committee (approval number: UATH/HREC/PR/233) and is in compliance with the Helsinki declaration. The minimum age for participation in the study was 18 years, but there was no upper age limit. Recruitment for the present study was initiated in December 2011 and data were obtained until August 2012. Of the two-hundred and twenty (220) subjects with hypertension, with or without heart failure, enrolled for the study, ten representing 4.5% of the total enrolment were excluded because they were either diabetic (1.8%), had regional wall motion abnormality on trans thoracic echocardiography (0.9%), had serum creatinine greater than $170\mu\text{mol/l}$ (1.4%) or had acute myocardial infarction (0.4%). Therefore, two-hundred and ten (210) were studied. One hundred and thirty three (133) were subjects with new referral for hypertension to the Cardiology Unit, Department of Medicine, of the University of Abuja Teaching Hospital, and another seventy seven (77) were subjects with hypertensive heart failure presenting to the same unit. **A study population of 210 subjects gave a study power of 100% and a chi-square value of 89.8 using a two-degree of freedom chi-square test.**

The University of Abuja Teaching Hospital, comprising three-hundred and sixty (360) beds, is the largest hospital serving the Federal Capital Territory (FCT) of Nigeria, which has a population of over two million. The Cardiology Unit has the services of three cardiologists, five interns in training, three house physicians and five trained nurses. The subjects were typically referred by both general and family physicians in primary and secondary healthcare settings, including private facilities. Subjects were, on average, public servants, traders, artisans, politicians, farmers, retired public servants and health workers.

Hypertension was defined according to the JNC VII guidelines (JNC et al 2004), while heart failure was diagnosed according to the European Society of Cardiology (ESC Task Force 2005) Guidelines, as shown in table 3.1 and functional status of the heart failure subjects was according to the guidelines of the New York Heart Association Functional classification (NYHA 1964). All subjects gave written informed consent to participate in the study.

Each subject had fasting blood sugar, fasting lipid profile, electrolyte, urea and creatinine and full blood count assessed. Blood chemical analysis was performed at a central certified laboratory. Fasting blood sugar and fasting lipid profile were analysed by auto analyzer (Erber Spectrophotometer, Boehringer GmbH, Mannheim, Germany). Each subject also had blood collected, processed and plasma stored at -80 degrees Celsius until assayed for NT-pro BNP. They also had a transthoracic echocardiography performed the same day that the sample was collected for NT-pro BNP.

3.2 Questionnaire

All the subjects completed a standard questionnaire. Due to the multiplicity of languages in Nigeria, the questionnaire was not translated into any of the local languages. The majority of the subjects were reasonably proficient in English language. Where there was need for interpretation, both medical and para-medical staff of the Cardiology Unit of the Department of Medicine of University of Abuja Teaching Hospital assisted. The questionnaire requested specific answers to date of birth, gender, occupation, background diagnosis of hypertension, background diagnosis of diabetes mellitus, history of angina pains, history alcohol consumption and history of smoking habits.

3.3 Anthropometric Measurements

The height and weight of the subjects were measured by the clinic nursing staff. Height and weight were measured with the participants standing, wearing indoor clothes with no shoes. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Body surface area in meters² (m²) was calculated as $(0.0001) \times (71.84) \times (\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725}$

3.4 Conventional Blood Pressure Measurements

Blood pressure measurements were obtained, according to standard guidelines, with a mercury sphygmomanometer (Accouson London). Systolic and diastolic blood pressures were measured by cardiologists at Korotkoff sounds I and V respectively. Blood pressure was measured at the right arm, three times after a 5-minute rest, with the patient in a sitting position, and the average of the three measurements was obtained. Pulse pressure was calculated as systolic blood pressure minus diastolic blood

pressure, while mean arterial pressure was calculated as a third of diastolic blood pressure plus pulse pressure.

3.5 Blood Measurements

Apart from blood samples for fasting blood sugar, fasting lipid profile, electrolyte, urea and creatinine and full blood count, another 10mls was collected from each patient for NT-pro BNP assay. The blood was transfused into EDTA tubes and samples were immediately centrifuged, plasma separated and then stored at -80 degrees Celsius until assayed. Samples were transported in dry ice and shipped to the Hatter Institute of Cardiovascular Research in Africa where the assay was carried out.

3.5.1 Plasma NT-pro BNP Assay

Plasma NT-pro BNP was measured by a standard electrochemiluminescence immunoassay. NT-pro BNP levels were measured from a banked aliquot from stored blood samples in triplicate. A sensitive and specific non-radioactive immunoluminometric (ILMA) assay based on competitive ligand binding was used. Stored samples were acidified with 1% trifluoroacetic acid (TFA) and loaded onto cartridges and eluted with 1% TFA containing 60% acetonitrile. The samples were lyophilised in a centrifugal evaporator and re-dissolved in assay buffer consisting of 0.1mol/L sodium phosphate (pH 7.4), 0.1% Triton X-100 for the measurement. NT-pro BNP concentrations were determined blind to the clinical details of a subject. Figure 3.1 shows a picture of the NT-pro BNP assay kit used for the study.

3.5.2 Plasma ST2 Assay

On patient enrolment, 20ml of venous blood was drawn into two separate tubes containing EDTA and Heparin, centrifuged and stored at -80 degrees Celsius. Soluble ST2 was measured by a sandwich double monoclonal antibody ELISA method, according to manufacturer's instructions (Presage ST2 assay, Critical Diagnostics, New York, New York) (Dieplinger et al 2009). Figure 3.2 shows the picture of the Soluble ST2 Assay kit which was used for the study. In brief, plasma samples and standards were incubated in microwells coated with anti-human ST2 antibody. After washing, peroxidise-

conjugated anti-human ST2 antibody was added into the microwell and incubated. After a second of washing, the peroxidise substrate was added and the optical density at 450nm was determined. A laboratory scientist, blinded to the clinical information, performed the ST assay. Although most reported studies refer to ST2 levels in serum, plasma ST2 was also increased in patients with acute heart failure (Dieplinger et al 2010). Furthermore, using the Presage ST2 assay as we did, soluble ST2 in frozen plasma samples has long-term stability for up to 18 months (Mueller et al 2008).



Figure 3.1: NT-Pro BNP Assay Kit



Figure 3.2: Soluble ST2 Assay Kit

3.6 Transthoracic Echocardiography

Echocardiography was performed using a commercially available ultrasound system (IVIS-60) which is shown in figure 3.5. Subjects were examined in the left lateral decubitus position using standard parasternal, short-axis and apical views. Studies were performed according to the recommendations of the American Society of Echocardiography (Sahn et al 1978) by an experienced echocardiographer. In our echocardiography laboratory, the intra observer concordance correlation coefficient amongst the three cardiologists involved in the study ranges from 0.76. 0.93, while that of the inter-observer concordance ranges from 0.82. 0.95. Measurements were averaged over 3 cardiac cycles. The left ventricular measurements taken include inter-ventricular septal thickness at end diastole (IVSd), the posterior wall thickness at end diastole (PWD), end diastolic diameter (EDD) and end systolic diameter (ESD). Left ventricular systolic function was calculated by Teichholz's formula (13). Figures 3.3 shows the parasternal long axis from one of the subjects. Left ventricular mass (LVM) was calculated using the formula of Teichholz (Teichholz et al 1976): $LVM = 0.8 [1.04$

$(IVSTd + LVIDd + PWT d)^3 + 0.6g]$. This has been shown to yield values closely related to necropsy left ventricular weight and that has good interstudy reproducibility ($r=0.90$). Relative wall thickness was calculated as $2 \times \text{posterior wall thickness} / \text{left ventricular internal dimension in diastole}$. Left ventricular hypertrophy was considered present when left ventricular mass index exceeded 49.2g/m^2 in men and 46.7g/m^2 in women (Devereux et al 1986, Palmieri et al 1999).

The one-hundred and thirty-three subjects (133) without heart failure were divided into four geometric patterns (Kolo et al 2008) after transthoracic echocardiography. Subjects with normal LV mass index and relative wall thickness, less than 0.44, were considered to have normal geometry, while those with increased LV mass index and relative wall thickness greater than 0.44, were considered to have concentric hypertension. On the other hand, subjects had eccentric hypertrophy when there was increased LV mass index but the relative wall thickness was less than 0.44, while subjects had concentric remodelling when there was normal left ventricular mass index but relative wall thickness greater than 0.44. Also in these one-hundred and thirty-three subjects without heart failure, electrocardiography data was analysed for LVH, and LVH was defined according to the classic criteria of Cornell and/or Sokolow-Lyon.

The left and right atria areas were measured at end-ventricular systole when the atria chambers were at their greatest dimension, and with the bases of both atria at their greatest dimensions. Left ventricular inflow velocities were measured using pulsed-wave Doppler from the apical 4-chamber view, with the sample volume located between the tips of the mitral valve leaflet during ventricular diastole. Figure 3.6 and 3.7 show the apical four-chamber view of two of the subjects. Peak velocity of early rapid filling (E), peak velocity of late filling caused by atrial contraction (A) and the interval from peak of E wave to its extrapolation to the baseline or deceleration time (DT) were measured. The ratio of peak E-wave to A- wave was calculated. Diastolic function was categorized using mitral inflow and Doppler Tissue Imaging parameters. Grade 3 diastolic dysfunction or restrictive filling pattern was defined as E/A ratio greater than 2, with deceleration less than 130 milliseconds. Grade 1 diastolic dysfunction was defined as E/A ratio less than 1 and a deceleration time of 220 milliseconds, while grade 2 diastolic dysfunction or pseudonormal filling was diagnosed when deceleration time was greater than 220 milliseconds and the E/A ratio was between 1-2. Right ventricular systolic function was assessed on echocardiography using M-mode recordings through the lateral tricuspid valve annulus for the purpose of measuring the tricuspid annular plane systolic excursion (TAPSE). TAPSE is a method used to measure the distance of

systolic excursion of the RV annular segment along its longitudinal plane, from a standard apical 4-chamber window. TAPSE represents longitudinal function of the right ventricle. It is inferred that the greater the descent of the base in systole, the better the RV systolic function. TAPSE (Figure 3.4) is usually acquired by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole (Jurcut et al 2010). A TAPSE value less than 15mm denotes right ventricular systolic dysfunction (Ghio et al 2010). In the seventy-seven subjects with heart failure, right ventricular systolic pressure was calculated using the formula Right Ventricular Systolic Pressure (RVSP) = $4(\text{TRV})^2 + \text{Right Atrial Pressure (RAP)}$. TRV reflects the difference in pressure between right ventricle and right atrium. The TRV was measured from the continuous wave Doppler of tricuspid regurgitant jet from apical four-chamber or from the parasternal right ventricular inflow view if the regurgitant jet was eccentric. The RAP was estimated from the inferior vena cava (Lang et al, 2005) as shown in table 3.2.

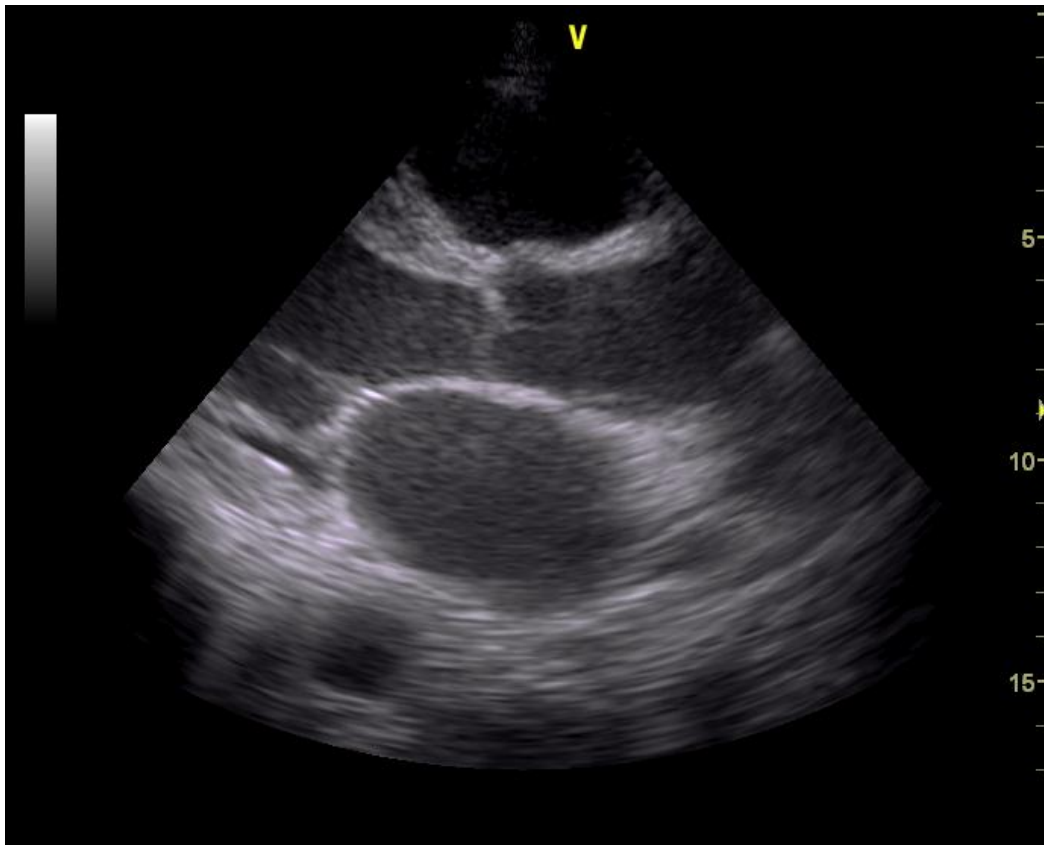


Figure 3.3 Parasternal Long Axis View for one of the Hypertensive Subjects

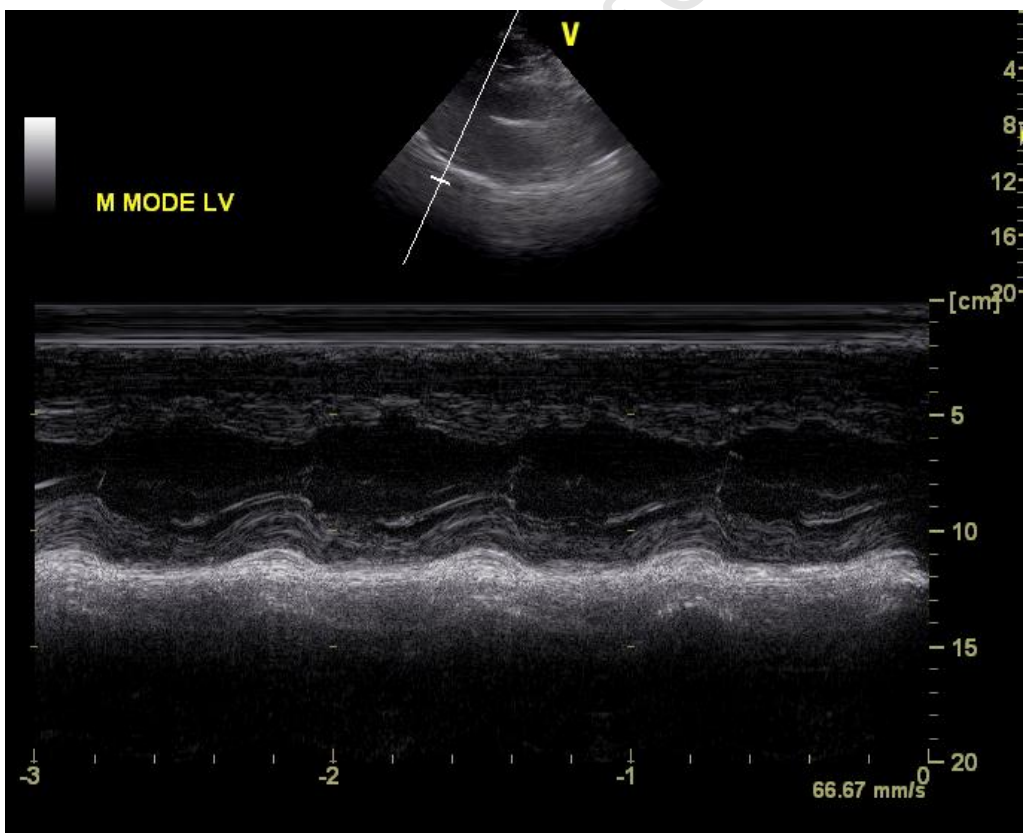


Figure 3.4 M-Mode of the Left Ventricle



Figure 3.5:IVIS Ultrasound Machine that used for theStudy

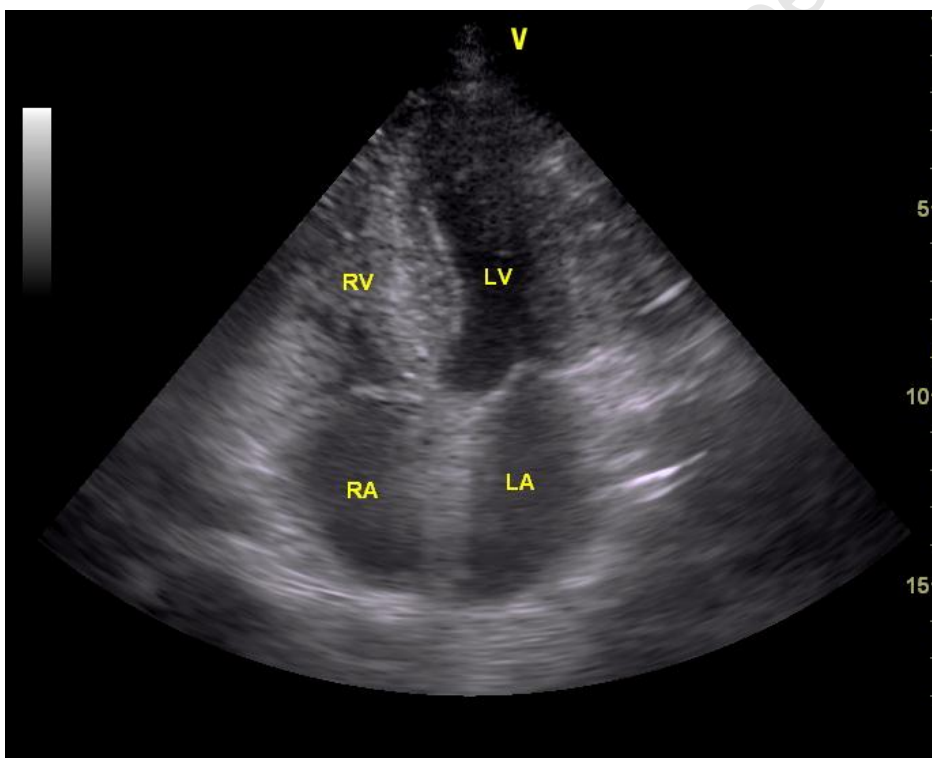


Figure 3.6 Apical four-chamber view of one of the hypertensive subjects with left ventricular hypertrophy

RV= Right Ventricle, RA=Right Atrium, LV=Left Ventricle, LA=Left Atrium

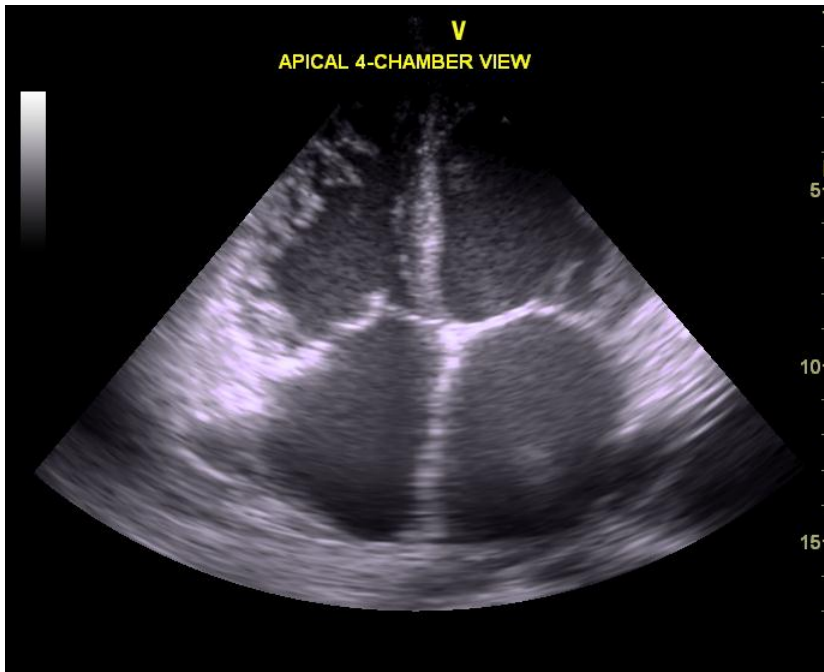


Figure 3.7 Apical Four-Chamber View of one of the subjects with Hypertensive Heart Failure showing Dilated Cardiac Chambers

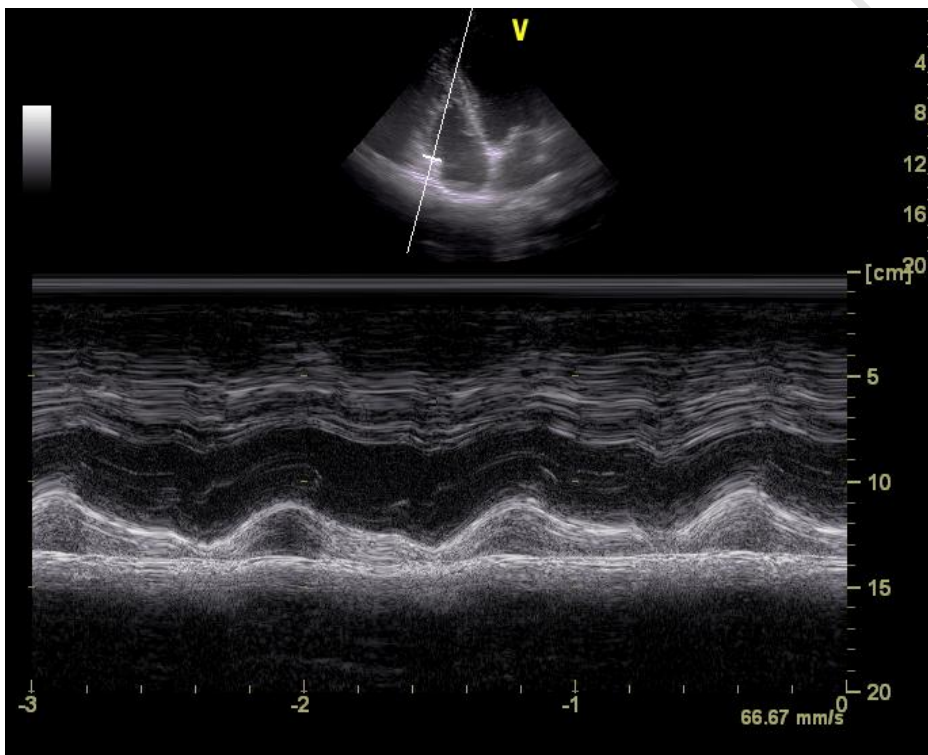


Figure 3.8 Top View: Apical four-chamber view with the M-mode cursor at the tricuspid annulus. Bottom View: M-Mode image of the tricuspid annulus from where TAPSE is measured

I. Symptoms of heart failure (at rest or during exercise) and
II. Objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) (at rest) and (in cases where the diagnosis is in doubt) and
III. Response to treatment directed towards heart failure

Table 3.1: Definition of Heart Failure according to the Recommendations of European Society of Cardiology

Criteria I and II should be fulfilled in all cases

Inferior Vena Cava Diameter	Change with Respiration	Estimated Right Atrial Pressure(mmHg)
Small < 1.5cm	Collapse	0
Normal 1.5cm-2.5cm	Decrease by > 50%	5
Normal	Decrease < 50%	10
Dilated > 2.5cm	Decrease by < 50%	15
Dilated with Dilated Hepatic Veins	No change	20

Table 3.2 Estimation of Right Atrial Pressure from the Inferior Vena Cava

3.7 Data Analysis

Statistical Analysis

SPSS software version 16.0 (SPSS Inc, Chicago, IL) and Medcal version 12.7 were used for statistical analysis. Continuous variables were expressed as mean \pm SD. Comparison of demographic, clinical, laboratory and echocardiographic parameters among the geometric patterns was performed by one-way ANOVA, with Sheffes post hoc test. Correlation coefficients were calculated by linear regression analysis with soluble ST2 and NT-pro BNP log-transformed to establish normality, and correlations

between soluble ST2, NT-pro BNP and continuous demographic, clinical, laboratory and echocardiographic were evaluated by Spearman regression. Multivariate linear regression analyses were performed with log transformed soluble ST2 and NT-pro BNP concentrations as dependent variables, with inclusion of demographic, clinical, laboratory and echocardiographic parameters and biomarkers. A 2-tailed p value < 0.05 was considered significant. Analyses of variation and operation characteristics were performed to determine the sensitivity and specificity of soluble ST2 and NT-pro BNP in differentiating the various spectrum of hypertension. **To determine the diagnostic reliability of NT-pro BNP and ST2, the receiver operating characteristics (ROC) curve was calculated and the cut-off points that maximised sensitivity and specificity were selected. The validity indexes between the two tests were compared with C-statistics.**

4.0 RESULTS

4. 1 Demographic, Clinical and Laboratory Characteristics of Subjects

4.1.1 Demographic, clinical and laboratory characteristics of the two-hundred and ten (210) subjects studied in Table 4.1.

The mean age of the study cohort was 50.3 ± 11.3 years. Subjects with hypertensive heart failure were the oldest, with a mean age of 53.0 ± 11.9 years, while those with hypertension without LVH were the youngest, with a mean age of 47.3 ± 11.0 years. Subjects with hypertensive heart failure had the lowest weight of the three study groups with a body mass index of $25.4 \pm 4.5 \text{ kg/m}^2$, as against $27.6 \pm 6.6 \text{ kg/m}^2$ for subjects with hypertension and LVH ($p\text{-value}=0.03$). Hypertensives with left ventricular hypertrophy had the highest levels of mean arterial pressure and pulse pressure, while subjects with hypertensive heart failure had the lowest levels. There was no significant difference amongst the study populations in the levels of fasting blood sugar, fasting lipid profile, urea, creatinine, haemoglobin concentration and white blood cell count.

Parameter	Hypertensive subjects N=83	Hypertensive Subjects with LVH N=50	P1	Hypertensive Heart Failure Subjects N=77	P2	P3
AGE, years	47.3(11.0)	51.1(10.2)	0.05	53.0(11.9)	0.35	<0.002
BMI, kg/m ²	27.9(5.3)	27.6(6.6)	0.76	25.4(4.5)	0.03	<0.001
FBS, mmol/L	4.84(0.55)	4.85(0.60)	0.96	4.93(0.60)	0.45	0.35
TC, mmol/L	5.03(0.9)	4.70(1.11)	0.07	4.52(1.04)	0.36	<0.001
LDLC, mmol/L	3.20(0.8)	3.07(0.95)	0.36	2.95(0.84)	0.46	0.037
HDL, mmol/L	1.26(0.4)	1.20(0.33)	0.35	1.15(0.29)	0.36	0.031
TG, mmol/L	1.42(0.7)	1.45(1.04)	0.84	1.25(0.29)	0.52	0.375
Creatinine,	91.60(21.9)	100.10(36.75)	0.10	104.73(27.71)	0.45	<0.001
PCV	39.3(3.5)	39.2(4.2)	0.95	39.0(5.5)	0.78	0.68
PP	64.1(15.0)	67.0(26.9)	0.43	54.3(17.4)	<0.002	<0.000
MAP	115.1(16.0)	120.6(26.7)	0.16	108.6(19.5)	<0.001	<0.000
NT-PRO BNP pg/ml	341.0(95.8)	353.2(161.4)	0.68	501.8(199.8)	<0.0002	<0.0001
ST2ng/ml	14.5(4.9)	23.0(8.33)	<0.001	134.7(57.3)	<0.0001	<0.0000

Table 4.1 Demographic, Clinical and Laboratory Characteristics of Subjects

P1=The p-value comparing hypertensive subjects with hypertensive subjects with left ventricular hypertrophy, P2= The p-value comparing hypertensive subjects with left ventricular wall hypertrophy and hypertensive heart failure, P3=The p-value comparing HT with HHF. BMI=Body Mass Index, FBS= Fasting Blood Sugar, TC=Total Cholesterol, LDLC=Low Density Lipoprotein Cholesterol, HDLC=High Density Lipoprotein Cholesterol, TG=Triglyceride, PCV=Packed Cell Volume, PP=Pulse Pressure, MAP=Mean Arterial Pressure

4.1.2 Clinical Features of the One-Hundred and Thirty Three Subjects without Heart Failure by the Four Left Ventricular Geometric Patterns in Table 4.2

Subjects with concentric remodelling were the oldest (average age 56.1 ± 8.4 years), versus subjects with normal geometry (average age of 46.3 ± 10.8 years; p -value < 0.004). Subjects with eccentric hypertrophy weighed the most (mean body mass index $29.6 \pm 5.0 \text{ kg/m}^2$ versus those with normal geometry (BMI, $25.4 \pm 4.1 \text{ kg/m}^2$; p -value < 0.003). Subjects with concentric hypertrophy had the second largest BMI ($28.7 \pm 5.4 \text{ kg/m}^2$) versus those with normal geometry (p -value $= 0.011$). There was no significant difference in the blood pressure profiles of the four groups.

4.1.3 Pattern of LV Geometry in the Subjects

Concentric remodelling was the most common form of geometry in 41.4% of cases, followed by eccentric hypertrophy in 30.8% of cases, then concentric remodeling in 14.3% of cases and normal geometry in 13.5% of cases (Fig 4.1). Figure 4.2 shows the pattern of distribution of left ventricular geometry by gender. 42.4% of the female population had concentric hypertrophy, as against 40.4% of the male population. The male population, however, had higher percentages of subjects with eccentric and concentric remodeling in 32.8% and 14.9% respectively, as against 28.8% and 13.6% respectively in the female population.

4.1.4 Clinical Profile of the seventy-seven Subjects with Hypertensive Heart Failure (Table 4.3)

Table 4.3 shows the clinical profile of the seventy-seven subjects with heart failure. The mean age of the subjects was 53.8 ± 13.2 years. There was no significant difference between the ages of the male and female subjects, nor was there a difference in the body mass index between male and female subjects. The men were more likely to smoke than the women (18.6% versus 2.5%, p -value < 0.0001), had better renal function with estimated glomerular filtration rate of $111.6 \pm 41.4 \text{ ml/min}$ versus $78.3 \pm 17.0 \text{ ml/min}$, p -value < 0.0001 and were more likely to be diabetic (5.0% versus 1.6%, p -value < 0.001). The women on the other hand were more likely to present with palpitations (57.7% versus 48.9%, p -value $= 0.02$). Serum ST2 and NT-pro BNP levels were similar in men and women.

Parameter	Normal Geometry	Concentric Hypertrophy	Eccentric Hypertrophy	Concentric Remodelling
Age, years	46.3±10.8	49.3±11.0	45.9±9.8	56.1±8.4*
Gender (%) F/M	15/12	42/40	28/33	13/15
BMI, kg/m ²	25.4±4.1	28.7±5.4*	29.6±5.0*	25.4±5.3
SBP, mmHg	151.1±20.0	158.5±27.2	148.0±22.4	145.3±19.0
DBP, mmHg	94.4±11.0	99.2±15.8	94.8±15.0	92.9±13.0
PP, mmHg	56.7±14.1	59.3±20.9	53.2±14.7	52.3±12.9
MAP, mmHg	118.1±15.5	122.4±21.9	128.8±16.2	123.3±13.9
Soluble ST2 ng/ml	14.3±5.4	20.4±8.4**	17.8±8.3	16.2±2.9
NT-pro BNP pg/ml	329.5±61.3	345±87.3	336.0±144.7	340±98.0
Serum Creatinine	86.1±20.9	98.7±36.1	93.0±24.0	93.0±18.9

Table 4.2 Clinical Features of the Four LV Geometric Patterns

*= Significantly higher compared to normal geometry, **= p< 0.002, M=Male, F=Female, BMI=Body Mass Index, SBP= Systolic Blood Pressure, DBP=Diastolic Blood Pressure, PP= Pulse Pressure, MAP= Mean Arterial Pressure

Parameters	ALL(N=77)	Male(N=54)	Female± (N=23)	P-value
Age	53.8±13.2	53.8±15.8	51.7±13.6	0.56
Smoking Habits	5(6.5%)	4(7.4%)	1(4.3%)	<0.001
DM	7(3.8%)	6(5.0%)	1(1.6%)	<0.001
Body Mass Index	24.30±7.0	24.2±7.6	24.5±5.9	0.86
Palpitations	94(33.3%)	58(48.9%)	36(57.7%)	0.02
Peripheral Oedema	115(63.2%)	72(60.7%)	43(67.9%)	NS
NYHA Class				
II	34(18.7%)	27(22.6%)	7(11.1%)	
III	114(62.6%)	70(58.8%)	44(69.8%)	
IV	34(18.7%)	22(18.6%)	12(19.1%)	
SBP	149.1±23.8	149.9±23.8	147.7±23.9	0.55
DBP	98.1±13.9	98.2±13.9	97.9±13.9	0.92
PP	55.8±16.2	56.4±16.8	54.7±15.0	0.52
MAP	101.3±16.4	101.2±17.2	101.5±15.0	0.89
FBS	5.3±2.2	5.2±2.0	5.4±2.4	0.58
Total Cholesterol	4.2±1.2	4.1±1.2	4.3±1.2	0.22
LDL Cholesterol	2.7±0.9	2.6±1.0	2.8±1.0	0.14
HDL Cholesterol	1.1±0.4	1.1±0.4	1.1±0.3	0.63
Estimated GFR	101.5±38.8	111.6±41.4	78.3±17.0	<0.0001
NT-pro BNP	501.7±199.8	513.0±208.5	478.7±184.7	0.58
Serum ST2	112.9±78.7	100.1±60.4	134.4±98.3	0.26

Table 4.3 Clinical Profile of the Subjects with Hypertensive Heart Failure

DM=Diabetes Mellitus, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, PP=Pulse Pressure, MAP=Mean Arterial Pressure, FBS=Fasting Blood Sugar, LDL=Low Density Lipoprotein, HDL=High Density Lipoprotein, GFR=Glomerular Filtration Rate, NT=N-Terminal, BNP=Brain Natruretic Peptide

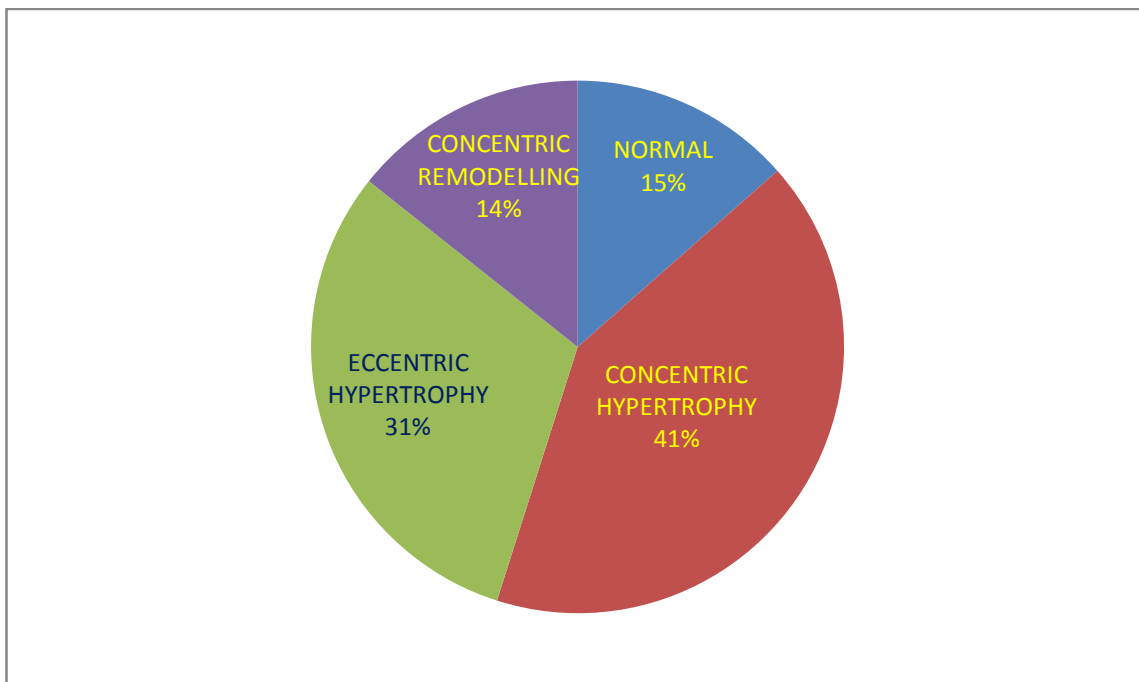


Figure 4.1 Pattern of Left Ventricular Geometry in the Subjects

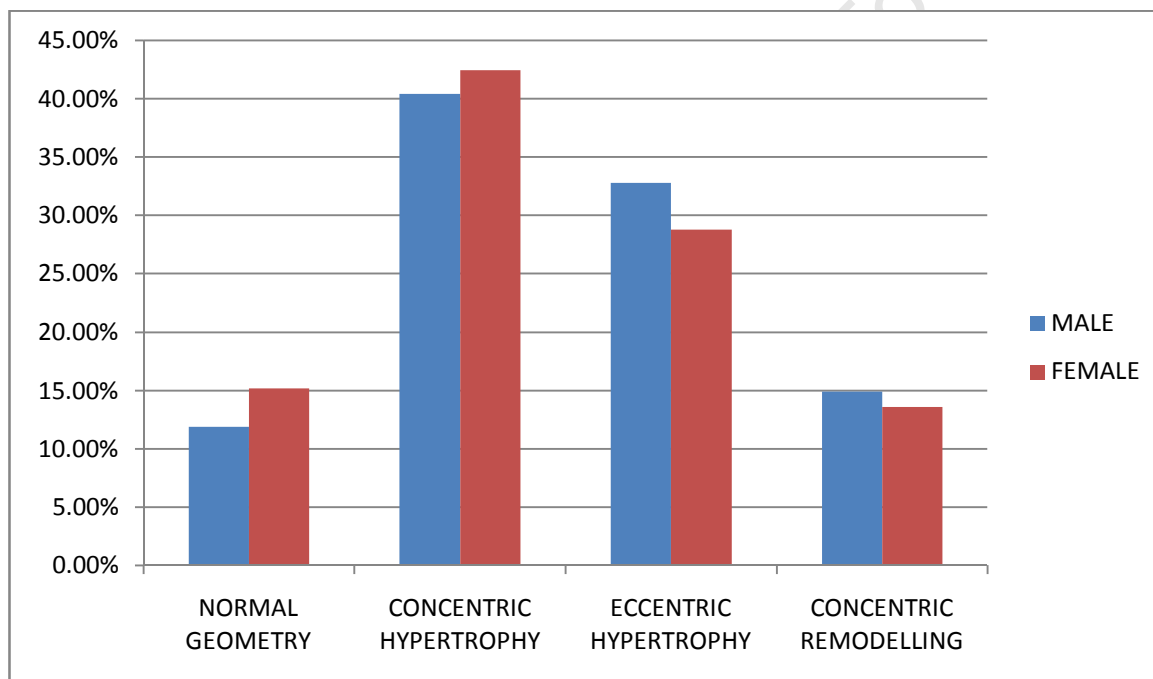


Figure 4.2 Pattern of Left Ventricular Geometry by Gender

4.2 Left Ventricular and Right Ventricular Geometric Changes Characterised by Echocardiography

4.2.1 Echocardiographic Characteristics of all the Subjects studied (Table 4.4)

Hypertensive subjects with LVH had significantly higher inter-ventricular and left ventricular posterior wall hypertrophy when compared with hypertensive subjects without left ventricular hypertrophy (p-value<0.001 and 0.001 respectively) and when compared with subjects with hypertensive heart failure (p-value<0.000 and 0.001). Hypertensive subjects with LVH also had higher left ventricular mass and left ventricular mass index, when compared with hypertensives without LVH and heart failure (p-value<0.001 respectively). They however have a smaller left ventricular mass, whether indexed or not, when compared with hypertensive heart failure subjects (p-value<0.001). Hypertensive subjects without LVH and left ventricular heart failure had a significantly higher left ventricular ejection fraction when compared with hypertensives with LVH (p-value of 0.02), and hypertensive heart failure subjects (p-value of < 0.001). Apart from the right atrial area, hypertensive heart failure subjects had a significantly higher chamber diameter. They also had the highest mitral E/A ratio and the lowest tricuspid annular plane pulmonary systolic excursion value.

4.2.2 Echocardiographic Characteristics of the four Geometric Patterns in One-Hundred and Thirty Three Subjects without Heart Failure in Table 4.5

Subjects with concentric LVH, eccentric LVH and concentric remodelling had higher IVSTd and PWTd, compared to subjects with normal geometry, while subjects with concentric LVH and concentric remodelling had higher RWT compared to subjects with normal geometry. LVM index was highest in concentric LVH, followed by eccentric LVH. LV internal diameter in both diastole and systole were higher in all other geometric patterns relative to normal geometry. Subjects with concentric hypertrophy had the lowest LV ejection fraction versus those with normal geometry ($70.7 \pm 18.6\%$ versus $76.7 \pm 18.6\%$; p-value= 0.02). Subjects with concentric remodeling had the smallest transmitral E/A (0.84 ± 0.28 versus 1.1 ± 0.29 , p-value <0.008) versus those with normal geometry, while those with concentric remodeling had the largest deceleration time (201.0 ± 45.6 millisec versus 158.9 ± 22.3 millisec; p-value <0.001) compared with normal geometry.

4.2.3 Echocardiographic Profile of the Seventy-Seven Subjects with Heart Failure by Gender in Table 4.6

Male subjects had significantly more hypertrophy involving the inter-ventricular septal wall and a trend towards a thicker left ventricular posterior wall than female subjects. They also had a more dilated left ventricle, especially in diastole, than female subjects. There was, however, no gender difference in the left ventricular mass indexed for height.

^{2.7} Using TAPSE, 33(42.9%) of the subjects had impaired RV systolic function.

University of Cape Town

VARIABLE	HT(83)	HT+LVH(50)	P1	HHF(77)	P2	P3
RVD	3.15(0.42)	3.10(0.43)	0.48	3.45(0.59)	<0.0005	<0.000
IVSD	0.92(0.15)	1.30(0.16)	<0.0002	0.91(0.19)	<0.0003	0.74
PWD	0.91(0.13)	1.26(0.20)	<0.0004	1.08(0.24)	<0.0001	<0.000
EDD	4.38(0.49)	4.37(0.95)	0.95	6.02(0.98)	<0.0003	<0.000
ESD	2.51(0.45)	2.72(0.95)	0.10	4.98(1.09)	<0.0001	<0.000
LVM	202.51(62.2)	296.1(151.8)	<0.000	488.3(163.9)	<0.0003	<0.000
LVM/ HT ^{2.7}	52.6(15.6)	73.0(35.1)	0.000	113.9(40.2)	<0.0004	<0.000
LAA	18.1(12.5)	20.6(4.5)	0.29	23.5(6.9)	<0.0001	<0.001
RAA	14.8(3.0)	15.04(3.95)	0.72	21.6(7.1)	0.15	<0.000
LVEF	76.8(14.0)	69.7(20.1)	0.02	32.2(13.6)	<0.0002	<0.000
ME	0.67(0.18)	0.66(0.18)	0.70	0.80(0.29)	<0.003	<0.000
MA	0.63(0.15)	0.67(0.20)	0.17	0.43(0.20)	<0.0004	<0.001
ME/MA	1.12(0.40)	1.1(0.43)	0.37	2.2	<0.0005	<0.000
DT	177.6(39.5)	188.3(53.4)	0.20	120.6(59.4)	<0.0006	<0.000
TAPSE	23.0(3.9)	21.5(5.0)	0.07	16.8(5.6)	<0.0005	<0.000

Table 4.4 Echocardiographic Characteristics of all the Subjects

HT=Hypertension without left ventricular wall hypertrophy, HT+LVH=Hypertension with left ventricular wall hypertrophy, HHF=Hypertensive heart failure, P1=p-value when HT and HT+LVH are compared and P2=p-value when HT+LVH and HHF are compared. P3= P-value when HT and HHF are compared. RVD=Right Ventricular Diameter in Diastole, IVSD=Inter-ventricular septal diameter in diastole, PWD= Posterior Wall Diameter in Diastole, EDD= End Diastolic Diameter, ESD= End Systolic Diameter, LVM= Left Ventricular Mass, ME= Early Mitral Inflow, MA= Late Mitral Inflow, LVEF = Left Ventricular Ejection Fraction, TAPSE= Tricuspid Annular Plane Systolic Excursion, DT=Deceleration time

Parameters	Normal Geometry	Concentric Hypertrophy	Eccentric Hypertrophy	Concentric Remodelling
RVD	3.14±0.35	3.19±0.47	3.20±0.34	3.20±0.44
IVSD	0.84±0.14	1.21±0.22*	0.97±0.18*	1.10±0.24*
PWD	0.78±0.08	1.20±0.18*	0.91±0.13*	1.00±0.15*
EDD	4.18±0.26	4.40±0.64*	4.80±0.71*	3.61±0.31*
ESD	2.33±0.34	2.69±0.70*	2.80±0.77*	2.07±0.30*
RWT	0.37±0.04	0.57±0.10*	0.38±0.04	0.57±0.12*
LVM/HT ^{2.7}	40.70±5.20	71.80±21.60*	65.40±32.30*	41.60±5.20
LAA	19.30±4.83	20.70±3.80	18.70±3.30	14.00±3.20
RAA	15.20±2.40	15.20±3.60	15.20±3.50	14.70±2.90
LVEF	76.70±18.60	70.70±18.60*	75.20±15.10	80.10±11.40
Mitral E/A	1.10±0.29	1.10±0.40	1.20±0.44	0.84±0.28*
DT	158.90±22.30	191.20±50.0*	172.0±38.50	201.00±45.60*
TAPSE	22.20±3.30	21.90±5.40	22.60±3.90	22.90±3.20

Table 4.5 Echocardiographic Characteristics of the four Geometric Patterns

*=Significantly higher compared to normal geometry ($p<0.001$), **=Significantly higher compared to concentric remodelling ($p<0.001$), RVD= Right Ventricular Diameter, IVSD=Inter Ventricular Septal Diameter in Diastole, PWD= Posterior Wall Diameter in Diastole, EDD= End Diastolic Diameter, ESD= End Systolic Diameter in Systole, RWT=Relative Wall Thickness, LVM= Left Ventricular Mass, HT=Height, LAA= Left Atrial Area, RAA= Right Atrial Area, LVEF= Left Ventricular Ejection Fraction, ME=Early Mitral Filling, MA=Atrial Filling, DT=Deceleration Time, TAPSE= Tricuspid Annular Pulmonary Excursion

Parameters	ALL(77)	MALE(54)	FEMALE(22)	P-value
RVD	3.4±0.6	3.5±0.6	3.2±0.5	0.22
Left Atrium	4.6±0.9	4.6±0.9	4.5±0.8	0.17
IVSD	1.1±0.3	1.1±0.2	1.0±0.3	0.03
PWD	1.1±0.2	1.2±0.2	1.1±0.2	0.07
EDD	5.8±1.1	5.9±1.1	5.5±1.1	0.04
ESD	4.7±1.3	4.9±1.2	4.5±1.3	0.07
LAA	24.5±7.0	24.5±6.7	24.4±7.5	0.95
RAA	22.3±8.1	22.6±8.0	21.7±8.5	0.50
LVMI	108.3±46.3	117.5±35.4	112.5±42.3	0.65
LVEF	35.2±17.5	34.4±16.8	36.6±18.7	0.58
ME	0.78±0.3	0.76±0.30	0.81±0.30	0.43
MA	0.49±0.2	0.49±0.2	0.49±0.1	0.25
ME/MA	2.2±1.3	2.0±1.2	2.2±1.4	0.96
DT	143.2±80.6	143.7±85.1	142.2±72.2	0.22
TAPSE	16.2±5.1	16.6±5.4	15.5±4.5	0.16
TAPSE< 15mm	33(42.9%)	54(40.7%)	10(41.7)	0.18
RVSP	31.4±10.5	31.4±10.4	31.3±10.5	0.97

Table 4.6 Echocardiographic Profile of the Subjects with Heart Failure by Gender

4.3 NT-Pro BNP versus ST2 as Biomarkers in the Hypertensive Cohort

4.3.1 Concentrations of Plasma NT-pro BNP in the Hypertensive Cohort

Figure 4.3 shows the different concentrations of plasma NT-pro BNP in the hypertensive cohort. There is no significant difference in the plasma concentrations of log transformed NT-pro BNP between the hypertensive subjects and subjects with hypertensive LVH, but there is a significant difference when hypertensive subjects, with or without left ventricular hypertrophy, are compared with those with heart failure. Figure 4.4 shows in receiver operation curve the differentiation of subjects with hypertension without LVH (HT) from those with heart failure (HHF), using NT- pro BNP. The sensitivity of NT-pro BNP in differentiating these two categories of subjects is 73.7%, while the specificity is 57.1%, with a cut-off value of 447.6pg/ml. The area under the curve (AUC) is 0.709, 95% confidence interval (CI) is 0.600-0.802 and p-value < 0.0002. Figure 4.5 similarly shows the receiver operation curve which differentiates subjects with hypertension and LVH (HTLVH) from hypertensive heart failure (HHF). The sensitivity of this differentiation is 49% and specificity is 83.3%. The area under the curve is 0.640, 95% confidence interval is 0.541-0.731 and p-value is 0.011.

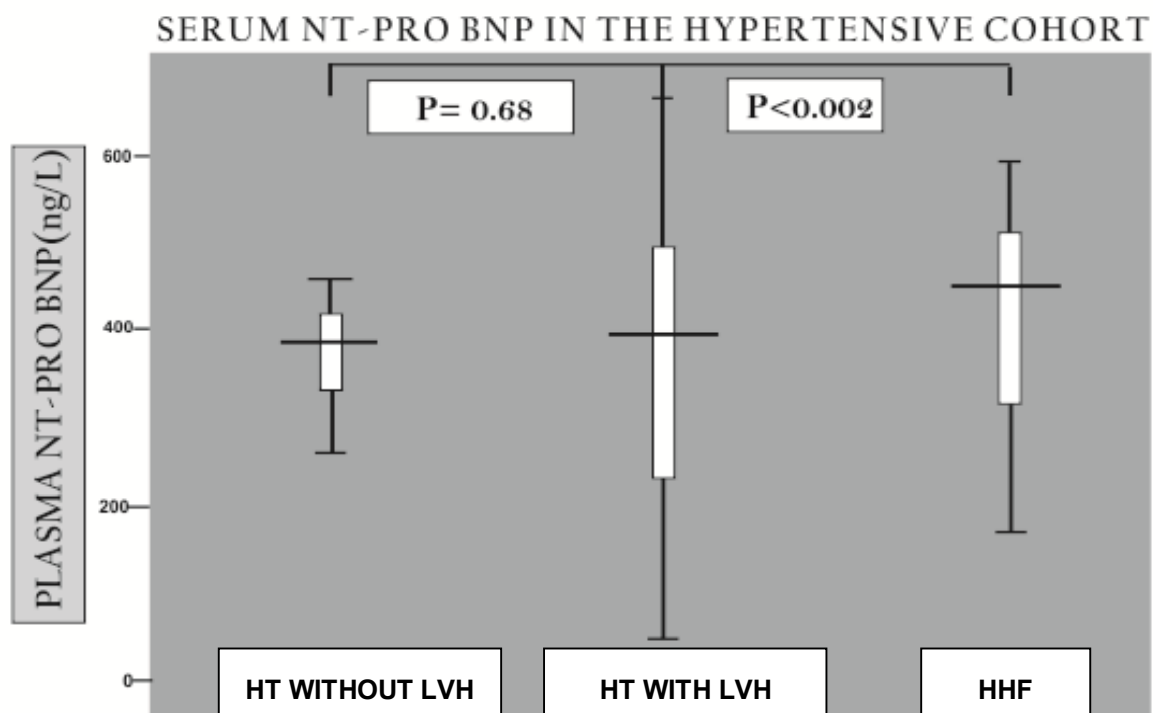


Figure 4.3: Box plot showing the different Concentrations of Serum NT-pro BNP in the Hypertensive Cohort

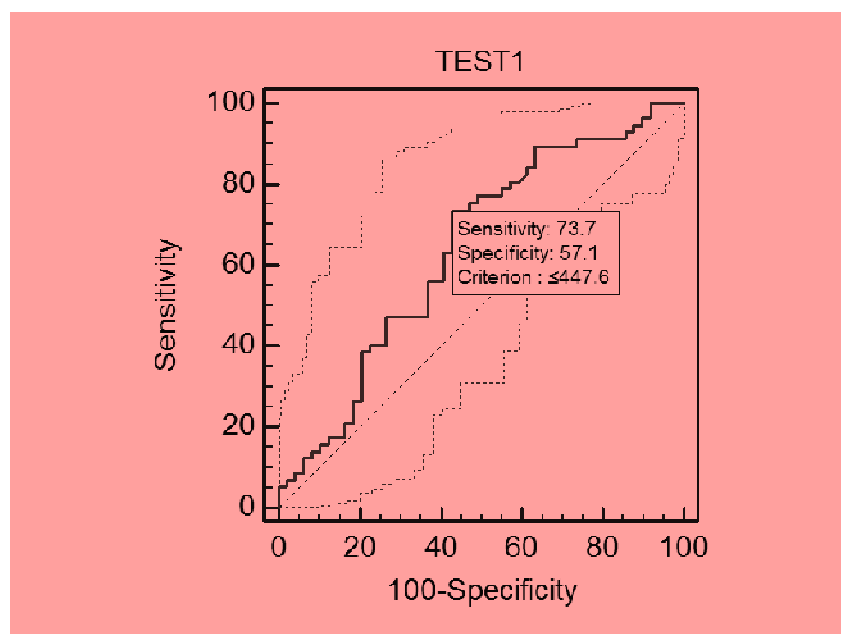


Figure 4.4: Receiver Operation Curve showing differentiation of Hypertension without LVH from Hypertensive Heart Failure

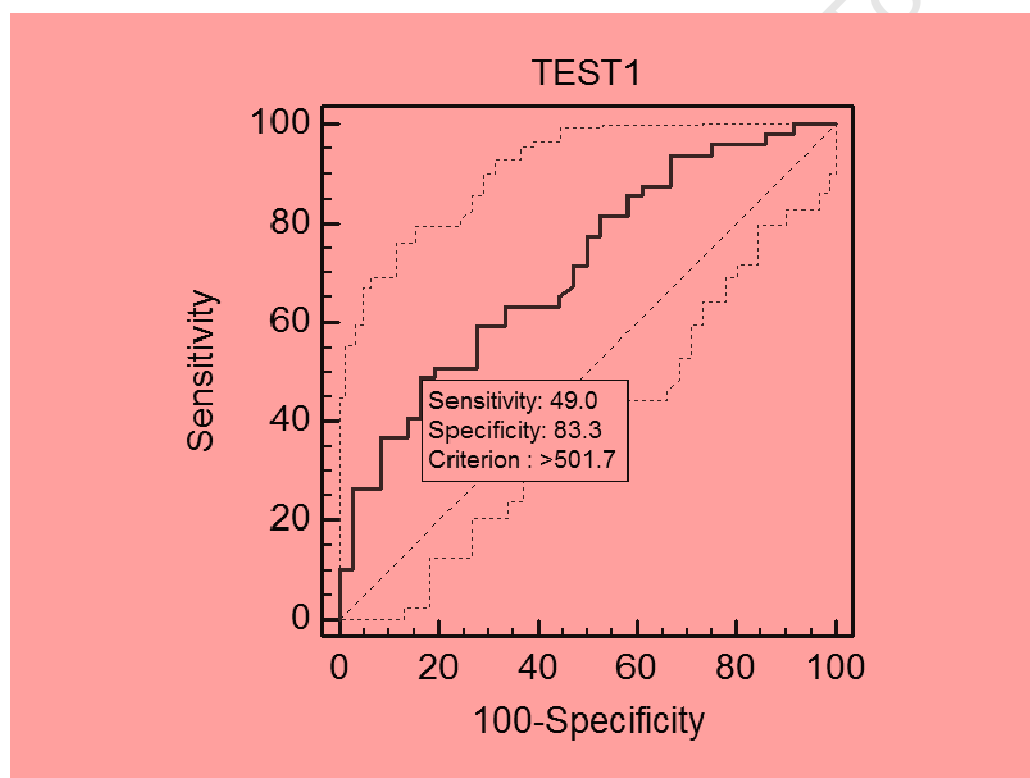


Figure 4.5: Receiver Operation Curve showing differentiation of Hypertension with LVH from Hypertensive Heart Failure

4.3.2 Clinical and Echocardiographic Correlates of NT-pro BNP

Pearson correlation analysis of clinical and echocardiographic variables with log transformed NT-pro BNP in the study population is shown in table 4.7. NT-pro BNP was significantly associated with left ventricular ejection fraction (p-value=0.01), but not with tricuspid annular plane systolic excursion. It was also significantly correlated with age (p-value< 0.04), pulse pressure and mean arterial pressure (p-value=0.002 respectively), systolic blood pressure (p-value=0.007), serum creatinine (p-value=0.038) and right atrial area. There was no significant correlation between NT-pro BNP with body mass index, right ventricular diameter in diastole, inter ventricular septal wall thickness in diastole, posterior wall diameter in diastole, left atria area, left ventricular mass index, transmitral E/A ratio, deceleration time and tricuspid annular plane systolic excursion

4.3.3 Independent Variables of NT-pro BNP

In multivariate linear regression analysis (Table 4.8) independent predictors of NT-pro BNP in the study population include left ventricular ejection fraction (t=2.11; p=0.037), right atria area (t=1.99,p=0.048) and left ventricular internal diameter in systole(t=2.21;p=0.029).

Parameters	Coefficient of association (r)	p-value
Age	0.17	0.04*
BMI	-0.07	0.40
Pulse Pressure	0.26	0.002*
Mean Arterial Pressure	0.26	0.002*
IVSDd	0.17	0.05
PWDd	0.08	0.36
LVIDD	0.16	0.05
LVIDS	0.21	0.01*
RVD	0.09	0.31
LAA	0.02	0.80
RAA	0.20	0.04*
LVM/HT ^{2.7}	0.09	0.30
Left Ventricular EF	-0.21	0.01*
Mitral E	0.02	0.79
Mitral A	0.12	0.15
Mitral E/A Ratio	0.08	0.35
Deceleration Time	0.14	0.09
TAPSE	-0.23	0.15

Table 4.7 Clinical and Echocardiographic Correlates of NT-pro BNP

IVSDd= Interventricular Septal Diameter in diastole, PWDd=Posterior Wall Diameter in diastole, LVIDs=Left Ventricular Internal Diameter in systole, RVD=Right Ventricular Diameter in diastole, LAA=Left Atrial Area, RAA=Right Atrial Area, TAPSE=Tricuspid Pulmonary Systolic Excursion, EF=Ejection Fraction, ME=Early Mitral Filling, A=Atrial or late mitral filling

Parameters	t	p-value
Left Ventricular Ejection Fraction	2.1	0.03
Left Ventricular Internal Diameter in Diastole	2.2	0.03
Right Atria Area	2.0	0.04

Table 4.8 Independent Co-variants of NT-pro BNP

4.3.4 Concentrations of Soluble ST2 in the Hypertensive Cohort

There was significant difference in serum soluble ST2 levels in the study cohort, with HHF subjects having significantly higher concentrations of serum soluble ST2, compared with subjects with HTLVH (134.7 ± 57.3 pg/ml versus 23.0 ± 8.33 pg/ml, p -value < 0.0001). On the other hand, subjects with HTLVH had higher concentrations when compared with HT subjects (23.0 ± 8.3 pg/ml versus 14.5 ± 4.9 pg/ml) as shown in figure 4.6. The sensitivity and specificity of differentiating HT from HHF were 82.4% and 100% respectively, with a cut-off value of 25.0 ng/ml, as shown in the receiver operation curve (ROC) in figure 4.7. The area under the curve is 0.98, confidence interval is 0.89-0.99 and p -value < 0.0001. On the other hand, the sensitivity of distinguishing HT from HTLVH were 87% and 56.7% respectively, with a cut-off value of 14.45 ng/ml, as shown in figure 4.8. The area under the curve is 0.72, 95% confidence interval is 0.57-0.85 and p -value is 0.004. Similarly, the sensitivity and specificity of distinguishing HTLVH from HHF were 76.5% and 100% respectively with a cut-off value of 38.0 ng/ml, as shown in figure 4.9. The area under the curve (AUC) is 0.90, 95% confidence interval is 0.79-0.97 and p -value < 0.0001.

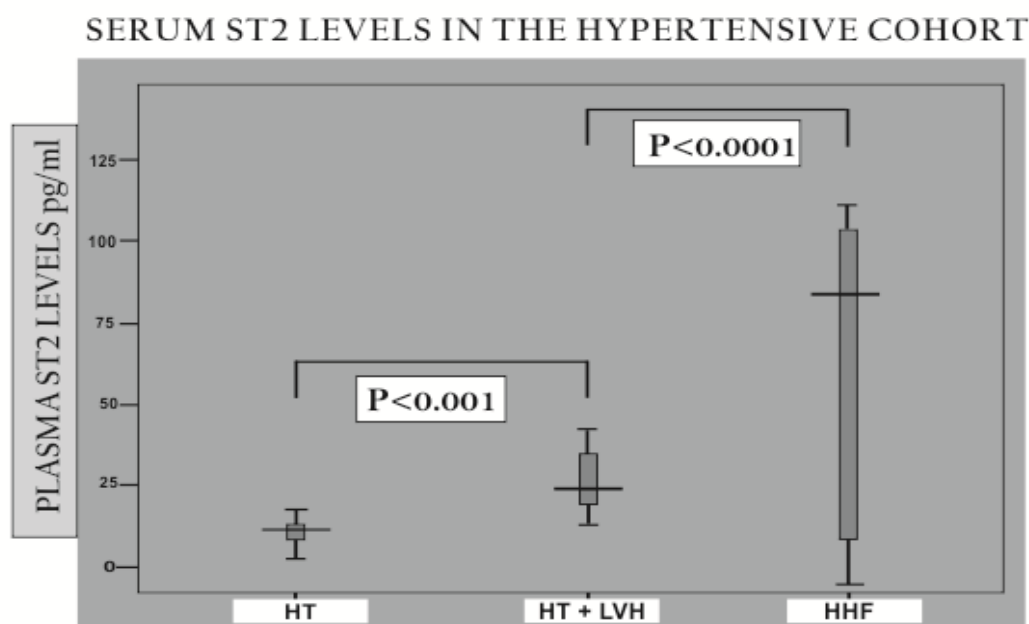


Figure 4.6: Box plot showing the different Concentrations of Soluble ST2 in the Hypertensive Cohort

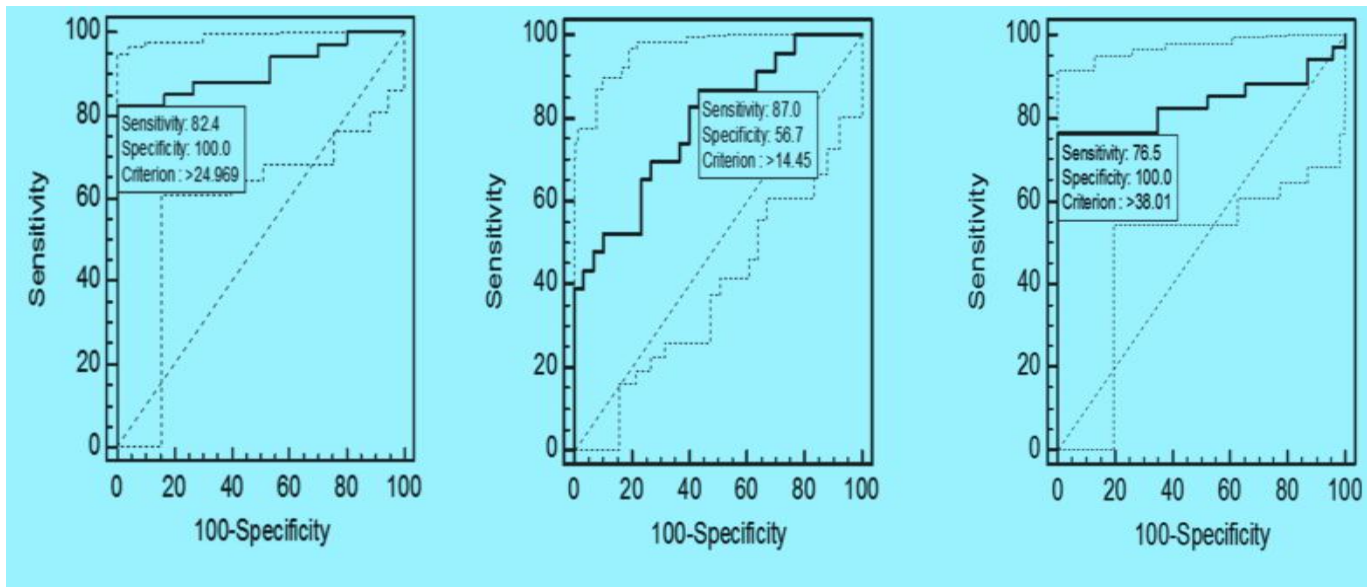


Figure 4.7

Figure 4.8

Figures 4.9

Figures 4.7, 4.8 and 4.9: Receiver Operation Curve Showing the differentiation of the various Hypertensive Cohorts using Soluble ST2

4.3.5 NT-pro BNP versus ST2 in distinguishing Hypertension with or without LVH from Hypertensive Heart Failure

Figures 4.10 and 4.11 show the comparison between soluble ST2 and NT-pro BNP in differentiating hypertension, with and without LVH, from hypertensive heart failure. Figure 4.10 shows that soluble ST2 is a better biomarker in differentiating HT from HHF with the difference between the areas of 0.30, 95% confidence interval of 0.146-0.452 and p-value < 0.0001. Figure 4.11 also shows that soluble ST2 is a better biomarker in differentiating HTLVH from HHF, with a difference between the areas of 0.27, confidence interval of 0.25-0.49 and p-value 0.01

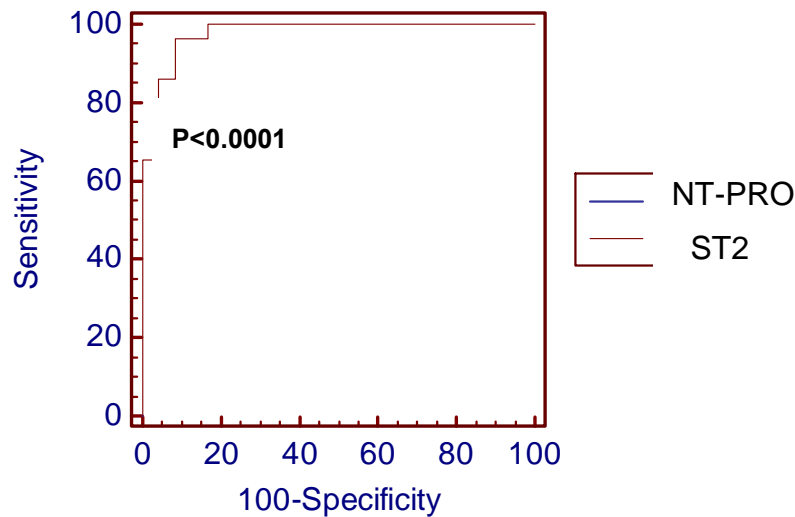


Figure 4.10: Comparison of ROC Curve of NT-pro BNP and ST2 in differentiating HT from HHF. Difference between areas under the curve (AUC)=0.30 and p-value<0.0001

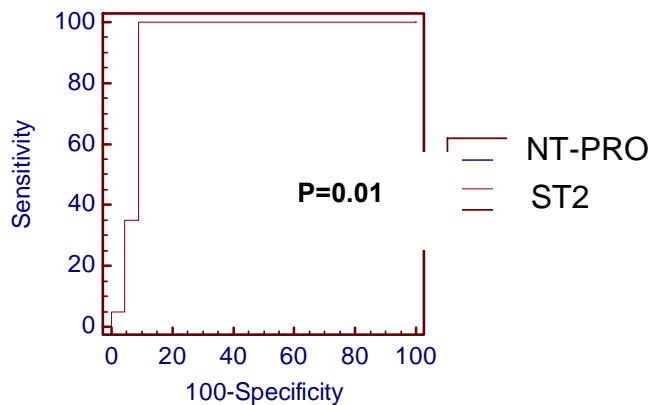


Figure 4.11: Comparison of ROC Curve of NT-pro BNP and ST2 in differentiating HTLVH from HHF. The differences in area under the curve (AUC)= 0.27 and p-value<0.01

4.3.6 Univariate Association between Log Transformed Soluble ST2 and some Clinical and Echocardiographic Parameters

Table 4.10 shows the univariate association between log transformed ST2 and clinical, laboratory and echocardiographic parameters. There was significant correlation between serum soluble ST2 and body mass index, inter-ventricular septal wall thickness in

diastole, posterior wall thickness in diastole, left ventricular internal diameter in diastole and systole, right atrial size, left ventricular mass index, left ventricular ejection fraction and transmitral E/A ratio. There was no correlation with left atrial area, and no correlation with blood pressure profiles. Of note, one of the most statistically significant associations was with left ventricular mass indexed for hypertension.

Parameters	R	PValue
Age	0.09	0.39
BMI	1.6	0.16
Pulse Pressure	0.26	0.02
Mean Arterial Pressure	0.23	0.04
IVSD	0.12	0.27
PWD	0.16	0.14
EDD	0.58	<0.0003
EDS	0.61	<0.0004
RVD	0.28	<0.008
LAA	0.48	<0.0004
RAA	0.46	<0.0005
LVM/ HT ^{2.7}	0.57	<0.0001
Left Ventricular EF	-0.60	<0.0002
Mitral E	0.42	<0.0005
Mitral A	0.26	0.02
Mitral E/A Ratio	0.43	<0.0006
Deceleration Time	0.48	<0.0004
TAPSE	0.15	0.20
NT-pro BNP	0.41	<0.0003

Table 4.9: Univariate Association between Log Transformed Soluble ST2 and some Clinical and Echocardiographic Parameters

RVD=Right Ventricular Diameter in Diastole, IVSD=Inter-Ventricular Diameter in Diastole, PWD=Posterior Wall Diameter in Diastole, EDD=End-Diastolic Diameter, ESD=End-Systolic Diameter, LVM=Left Ventricular Mass, LAA=Left Atria Area, RAA=Right Atria Area, EF=Ejection Fraction, ME=Early Mitral Filling, MA=Late Mitral Filling, TAPSE=Tricuspid Annular Plane Systolic Excursion, R=Coefficient of correlation for serum ST2 and variables

4.3.7 Multivariate Analysis of Independent Co-variants of Log Transformed Soluble ST2 in Table 4.11

In a multivariate analysis (table 4.8), the independent co-variants of serum soluble ST2 concentrations were found to be LV ejection fraction (beta=0.61; $p<0.0002$), LV mass indexed for height ^{2.7} (beta=0.56, $p<0.0001$), left internal diameter in systole (beta=0.61, $p<0.0004$) and pulse pressure (beta=2.5, $p=0.01$).

Table 4.10: Multivariate Analysis of Independent Co-variants of Log Transformed Soluble ST2

Parameters	Standardized Coefficient(β)	P-value
Left Ventricular Ejection Fraction (%)	0.56	<0.0001
Left Ventricular Internal Diameter in Systole	0.61	<0.0003
Left Ventricular Mass Index for HT 2.7	0.56	<0.0001
Pulse Pressure (mmHg)	0.25	0.01

4.4 Differentiation of Left Ventricular Geometric Patterns and Right Ventricular Function by NT-Pro BNP and ST2 and Echocardiography

4.4.1 Left Ventricular Geometric Pattern and Cardiac Biomarkers

Subjects with concentric hypertrophy had the highest concentrations of soluble ST2 (mean 20.4 ± 8.4 pg/ml) versus subjects with normal geometry (14.3 ± 5.4 pg/ml; p -value=0.002), as shown in table 4.5. The sensitivity of soluble ST2 in differentiating concentric hypertrophy from normal geometry was 68.2% and the specificity was 88.2% at a cut-off mark of 17.4ng/ml (Fig 4.12). There were no significant differences in the soluble ST2 levels amongst the other geometric patterns.

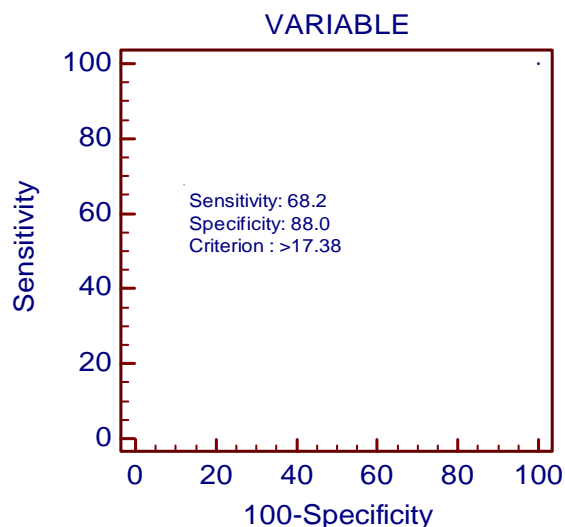


Figure 4.12: Receiver Operation Curve Showing the Sensitivity and Specificity of Soluble ST2 in Differentiating Concentric Hypertrophy from Normal Geometry

4.4.2 Diagnostic Accuracy of ST2 compared with Electrocardiography in Detecting LVH in Hypertensive Subjects without Heart Failure

Table 4.11 shows that 8(16%) of subjects with echocardiographic diagnosis of LVH had LVH using electrocardiographic criteria of Cornell and/or Sokolow-Lyon, while 4(4.8%) of those without LVH had LVH on ECG. Table 4.13 compares the sensitivity, specificity, positive and negative predictive values of soluble ST2 and ECG in diagnosing LVH. We found that the diagnostic accuracy of soluble ST2 was greater than that of electrocardiography study as evidenced by higher sensitivity and negative predictive value for this marker.

4.4.3 The Relationship between TAPSE and various echocardiographic and laboratory parameters.

Table 4.12 shows the relationship between right ventricular systolic function, as assessed by TAPSE, and various echocardiographic and laboratory parameters. Left atrial diameter, areas of both atria, left ventricular end-diastolic and end-systolic

diameters, left ventricular mass index, right ventricular systolic pressure, left ventricular ejection fraction and transmitral E/A ratio were found to correlate significantly with TAPSE. There was, however, no significant correlation between TAPSE and cardiac biomarkers.

4.4.4 The relationship between right ventricular systolic pressure and cardiac biomarkers

Table 4.13 shows the relationship between right ventricular systolic pressure and cardiac biomarkers. Both serum ST2 and NT-pro BNP were significantly correlated with right ventricular systolic pressure.

VARIABLE	HT(83)	HT+LVH(50)	P1
RVD	3.15(0.42)	3.10(0.43)	0.48
IVSD	0.92(0.15)	1.30(0.16)	<0.0002
PWD	0.91(0.13)	1.26(0.20)	<0.0004
EDD	4.38(0.49)	4.37(0.95)	0.95
ESD	2.51(0.45)	2.72(0.95)	0.10
LVM	202.51(62.2)	296.1(151.8)	<0.000
Soluble ST2(ng/ml)	14.5(4.9)	23.0(8.33)	<0.001
NT-PRO BNP(pg/ml)	341.0(95.8)	353.2(161.4)	0.68
LVH on ECG	4(4.8%)	8(16.0%)	<0.001

Table: 4.11: Biomarkers, Electrocardiographic and Echocardiographic

Characteristics of the subjects without Heart Failure

RVD=Right Ventricular Diameter, IVSD=Inter-ventricular Septal Thickness in Diastole, PWD=Posterior Wall Diameter in Diastole, EDD=End-Diastolic Diameter, ESD=End-Systolic Diameter, LVM=Left Ventricular Mass

	ECG% (95% CI)	ST2(>14.45ng/ml)% 95% CI	P-value
Sensitivity	16.0(8.6-23.8)	87.0(75.8-96.4)	<0.001
Specificity	95.2 (83.8-99.7)	56.7(48.7-65.7)	<0.001
PPV	51.6(19.9-82.4)	40.1(28.7-52.3)	<0.001
NPV	77.2(68.8-84.3)	92.9(83.2-97.9)	<0.001

Table 4.12: Indexes of Diagnostic Validity for Electrocardiography and ST2 in Left Ventricular Hypertrophy

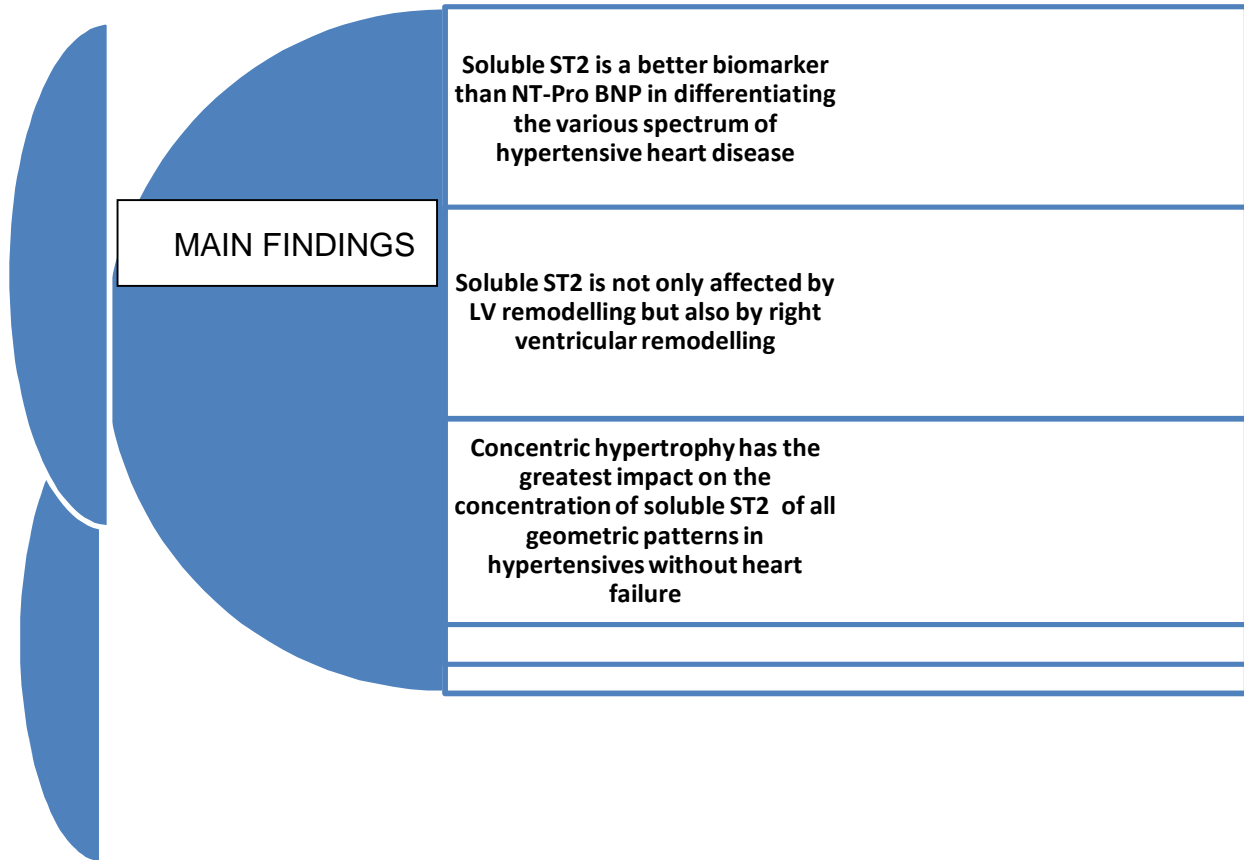
PPV= Positive Predictive Value, NPV=Negative Predictive Value

Table 4.13: Relationship between TAPSE and various echocardiographic and laboratory parameters.

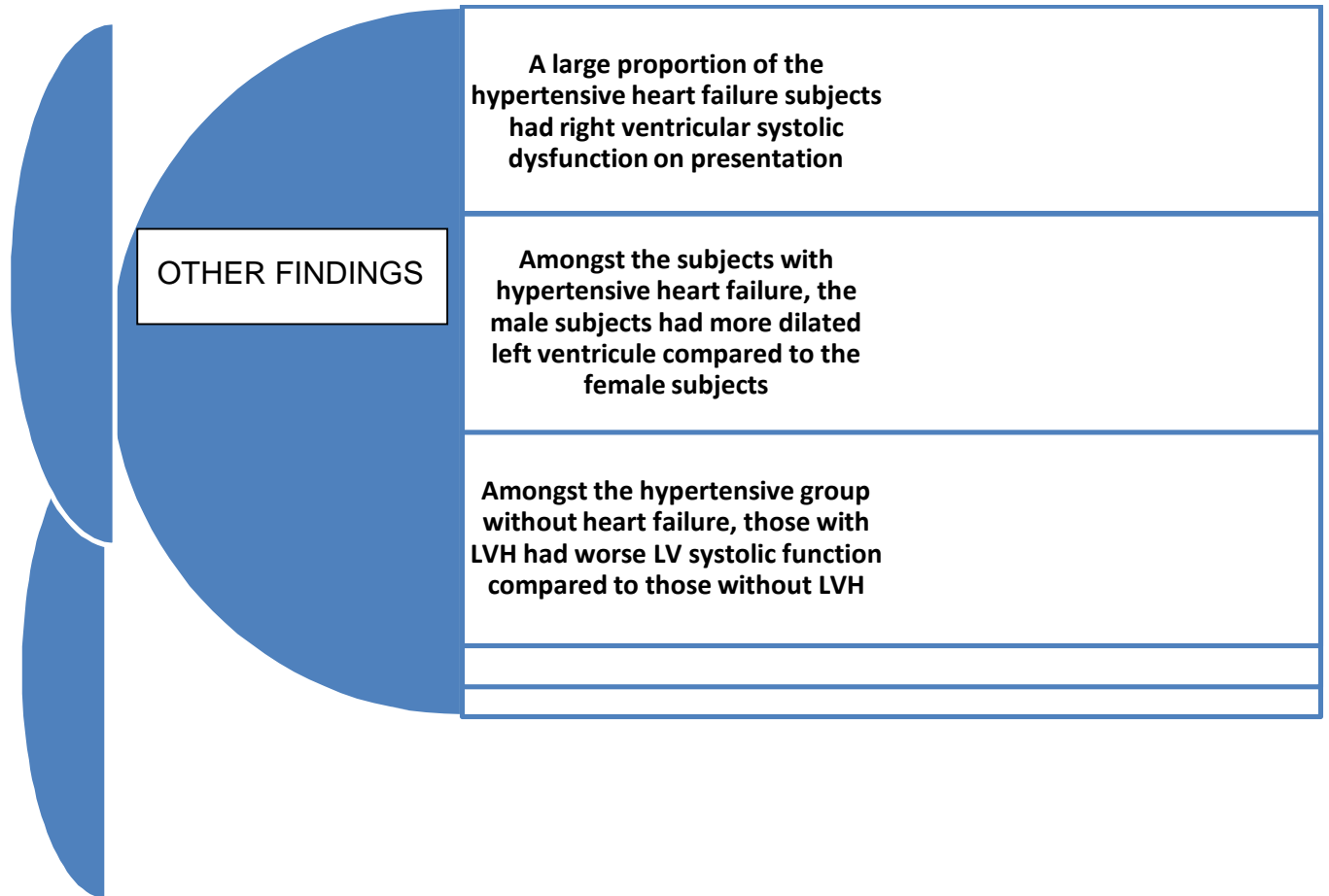
Parameters	Pearson Correlation	P-value
Left Atrial Diameter	-0.54	<0.0001
EDD	-0.47	<0.0001
ESD	-0.55	<0.0001
LVM/HT ^{2.7}	-0.34	<0.0001
LVEF	0.60	<0.0001
Mitral E/A	-0.39	<0.0001
Left Atrial Area	-0.24	0.02
Right Atrial Area	-0.44	<0.0001
RVSP	-0.74	<0.0001
RVD	-0.035	0.77
Soluble ST2	0.04	0.68
NT Pro BNP	0.000	0.99

EDD=End-Diastolic Diameter, ESD= End-Systolic Diameter, LVM=Left Ventricular Mass, HT=Height, LVEF=Left Ventricular Ejection Fraction, E=Early Filling, A=Atrial Filling, RVSP= Right Ventricular Systolic Pressure, RVD=Right Ventricular Diameter

Summary of Results



Summary of Results



5.0 Discussion

5.1 Characteristics of the study Population

This study documented the clinical profile of two-hundred and ten (210) hypertensive subjects, with or without heart failure, presenting to a tertiary institution in Abuja, Nigeria. We found the patients to be middle-aged, with a mean age of 47.3 ± 11.0 years. This is in keeping with previous studies which show that the complications of hypertension tend to occur more often, and at an earlier age, in black populations compared to Caucasians (Cruickshank JK et al 1980, Shulman NB et al 1991, Onwuanyi A et al 1998). Our demographic data also show that the subjects with hypertensive heart failure were much younger, with a mean age of 53.0 ± 11.9 years, compared to the developed countries where heart failure is a disease of the elderly, with an average age of 76 years (Goldberg et al 2007; Vasan et al 1999). Hypertensive heart failure presenting in a relatively young cohort in this Nigerian population is a further reflection of the presentation of the complications of hypertension at an early stage. Long distances and, often, lack of funding to cover the travel fare, are important aspects of late presentation to health care (Mocumbi et al 2012). This presentation of hypertensive heart failure at a relatively early age has the potential to undermine national productivity, as a consequence of the number of active life years lost by the most active workforce of the population, with important consequences to the entire family.

The three hypertensive groups were overweight, with a mean body mass index ranging from 25.4 kg/m^2 to 27.9 kg/m^2 . The subjects with heart failure had the lowest body mass index of 25.4 kg/m^2 , which is in keeping with previous reports, as heart failure is often associated with weight loss (Pocock et al 2008). The group with heart failure also had the lowest mean arterial blood pressure level and this can, in part, be attributed to the fact that these subjects often present with dilated left ventricular chambers and poor systolic function, thereby reducing cardiac output. Even though the average creatinine level was normal, as subjects with elevated creatinine were excluded from the study, the cohort with heart failure had significantly higher serum creatinine compared to hypertensive subjects without LVH. The possible explanation for this is both congestion and low renal perfusion from poor left ventricular systolic function in these subjects (Guglin et al 2011). Anaemia was not a common problem in this hypertensive cohort, with a mean packed cell volume of 39.0% in the study population. This can be partly explained by the fact that subjects with chronic kidney disease were excluded from this study as it is a well

known fact that chronic kidney disease is the most common cause of anaemia in hypertensive subjects in sub-Saharan Africa (Alebiosu CO et al 2006). Subjects with diabetes mellitus were also excluded from the study, accounting for the mean fasting blood sugar of 4.8mmol/l seen in our study cohort. Lastly, the prevalence of smoking in our heart failure subjects was considerably lower, compared to that in the developed nations and even lower in our female population, as shown in table 4.3. This is likely to have contributed to the lower prevalence of coronary artery disease in our environment.

5.2 Left and Right Ventricular Changes Characterised by Echocardiography

In this study, both the left and right ventricular structure and function were assessed. We found that 37.6% of the one-hundred and thirty-three subjects without heart failure had echocardiographic LVH, in keeping with previous studies in black hypertensive subjects. For example, Post et al (Post et al 2003) found an echocardiographic prevalence of 30% among 309 hypertensive African American men aged 18-54 years while Koren et al (Koren et al 1993) reported a prevalence of 41% in 47 black subjects with uncomplicated hypertension. Subjects with hypertensive heart failure had significantly more dilated left atrium and left ventricle, when compared with subjects without heart failure. They also had significantly more dilated right cardiac chambers. The larger right-sided cardiac chambers in these subjects implies that a significant proportion of our heart failure patients already have right ventricular dysfunction on presentation as right atrial and right ventricular sizes have been reported as markers of right ventricular dysfunction (Graspa J et al 2012, Ghio S et al 2010). This may, therefore, partly explain the poor prognosis of hypertensive heart failure in sub-Saharan Africa (Isezuo AS et al 2000) as it is well known that ventricular size and function are prognostic markers in left-sided heart failure (Dini FL et al 2012). There is, therefore, the need to investigate the effect of right ventricular dysfunction on prognosis in our hypertensive heart failure subjects. As expected, our cohort with heart failure had the worst left ventricular systolic function. We also found that subjects with HTLVH had significantly lower left ventricular ejection fraction, when compared with HT subjects which had been previously reported in hypertensive subjects (Schillac G et al 2002).

5.3 BNP versus Soluble ST2 as Biomarkers in the Hypertensive Cohort

The results of this study have shown that even though serum ST2 and NT-pro BNP can be very useful in distinguishing subjects with HTLVH from those with HHF, in keeping with a previous study (Talwar et al 2000), it is only serum ST2 that differentiates HT from HTLVH. These have been shown in figures 4.3 and 4.6. The significantly higher concentrations of serum soluble ST2 in subjects with HTLVH compared to those with HT, and significantly higher concentrations of plasma ST2 in HHF subjects compared to HTLVH subjects, is not surprising as serum ST2 concentration correlates well with wall tension and LV ejection fraction, both of which are caused by hypertensive LVH and hypertensive heart failure respectively (Sabatine et al 2008; Diez et al 2008). At a molecular level, the varying degree of mechanical strain imposed on cardiac myocytes (Weinberg et al 2002) by these three conditions could be postulated to explain the links between the ST2 concentrations and the clinical pictures. The mechanism of secretion of ST2 in hypertensive heart disease spectrum could thus be linked to cardiomyocyte hypertrophy and fibrosis which are prominent features of hypertensive LVH, and apoptosis which is a prominent feature of hypertensive heart failure (Sanada et al 2007; Seki et al 2009). Plasma ST2 correlated well with LV mass index in our hypertensive cohort, with LV mass indexed for height being an independent predictor of the concentration of serum soluble ST2 ($\beta=0.56$, $p\text{-value}<0.0001$), as shown in table 4.11, but there was no significant correlation between NT-pro BNP and LV mass index ($r=0.09$, $p\text{-value}=0.30$), as shown in table 4.8. In a previous study in hypertensive subjects which used serum NT-pro BNP as a biomarker, there was a poor correlation between LV mass index and NT-pro BNP(13). Thus, ST2 may be a better biomarker in differentiating the various components of the spectrum of HT, HTLVH and HHF from each other. Also on head-to-head comparison using differences in areas under the curve, ST2 was found to be a better biomarker than NT-pro BNP in differentiating HT from HHF($p<0.0001$) and HTLVH from HHF($p=0.01$), as shown in figures 4.10 and 4.11. LV ejection fraction was a predictor of plasma concentrations of soluble ST2. Even though it is known that LV ejection fraction is a strong predictor of serum soluble ST2 concentration (Shah et al 2009), our study is the first to demonstrate this relationship in a cohort of hypertensive subjects. Therefore, the diagnostic role of serum soluble ST2 is not limited to heart failure of only ischemic aetiology, but may also extend across all types of heart failure. Since LV ejection is a strong prognostic-factor in heart failure (Sanada et al 2007; Karaye et al 2008), our data therefore suggest that plasma ST2 could be a good prognostic marker of heart failure in hypertensive subjects.

A second important finding was that ST2 correlated well with right atrial area ($r=0.46$, p -value <0.0001) and less significantly with right ventricular diameter ($r=0.26$, p -value $=0.0008$), while NT-pro BNP correlated weakly with right atrial area ($r=0.2$, p -value $=0.04$) and did not correlate significantly with right ventricular diameter.

Daniel (Daniel et al 2010) had previously shown that serum soluble ST2 correlates well with the size of the right ventricle and is a predictor for mortality. Our results in this study have demonstrated a relationship between soluble plasma ST2 with ventricular sizes in a population of hypertensive subjects with or without heart failure.

We also showed an association between serum soluble ST2 and all the echocardiographic LV diastolic function parameters, in keeping with the findings of Shah (Shah et al 2011), who found an association between ST2 and echocardiographic LV diastolic parameters. They found serum ST2 to be a strong predictor of mortality in patients with acute dyspnoea, especially in those with preserved LV ejection fraction. Therefore, plasma ST2 is not only correlated with systolic function, but also with diastolic function in a cohort of our hypertensive subjects. On the other hand, there was no significant correlation between NT-pro BNP and all indices of diastolic function assessed in our study cohort, similar to previous studies (Fruhwald et al 1999).

In addition, levels of NT-pro BNP correlated with age (Redfield et al 2002) and serum creatinine levels as in previous reports (Sriswasdi et al 2010). ST2 levels did not, however, correlate significantly with either age or serum creatinine, which is another reason ST2 might be a better marker than NT-pro BNP, as it is less likely to be affected by confounders such as age and renal dysfunction.

Furthermore, we found a correlation between serum soluble ST2 levels and serum NT-pro BNP, with a correlation coefficient of 0.41 and a $p < 0.0002$. This is similar to the findings of Shah et al (34), who found a correlation ($p = 0.009$) between serum soluble ST2 and serum NT-pro BNP.

Overall, our study has shown that serum ST2 is a very useful biomarker in differentiating the various spectrum of hypertension. We have also shown that serum ST2 does not only complement the role of NT-pro BNP in differentiating the various spectrum of hypertension, but might be a better biomarker than NT-pro BNP in this regard. Our findings will assist in distinguishing the three prognostic patterns of uncomplicated hypertension from two of its major cardiac complications, and may also become useful in the choice of specific antihypertensive medications. It is well known that medication such as angiotensin converting enzyme inhibitors (Shimamoto et al 1996), angiotensin

receptor blockers (Cuspidi et al 1996), beta-1-selective blockers (Cifkova R et al 1987) and long-acting calcium channel blockers (Nalbantgil et al 1996) have been found to regress the LVH, while thiazide diuretic monotherapy which is a common prescription pattern in our setting (Kazeem et al 2005), has not been found to do so (Strauer et al 1985). In a meta-analysis of eighty (80) trials (shown in figure 5.1) with one-hundred and forty-six (146) treatment arms and a study population of 3767, and 17 placebo arms with a population of 346, after adjusting for treatment duration and change in diastolic blood pressure, there was significant difference ($p=0.004$) in left ventricular mass regression among anti-hypertensive medication classes. Angiotensin II receptor blockers (ARBs) reduced LVM by 13%, calcium channel blockers (CCBs) by 11%, angiotensin converting enzyme inhibitors (ACEIs) by 10%, while diuretics and beta-blockers only reduced LVM by 8% and 6% respectively. It was concluded that in pair wise comparisons, ARBs, CCBs and ACEIs were more effective in reducing LVM than beta-blockers and diuretics.

Since the diagnosis of ischemic heart disease was made clinically using history and electrocardiography, with no myocardial perfusion imaging and coronary angiography performed, it is possible that subtle coronary artery disease might have been missed. **However, with the low prevalence of clinical myocardial infarction and the high cost of myocardial perfusion and coronary imaging in this environment we did not think it was justifiable for these subjects to have these investigations.**

Serum soluble ST2 does not only complement the role of NT-pro BNP as a biomarker in differentiating hypertension itself from two of its major cardiac complications, but it is an excellent biomarker in this regard. The usefulness of soluble ST2, therefore, extends beyond ischemic heart disease and cardiomyopathies to hypertensive heart disease.

5.4 Differentiation of Left Ventricular Geometric Patterns by NT-pro BNP and ST2

Concentric hypertrophy was the most common geometric pattern in our study cohort (Figure 4.1), and just slightly more common in the female population, compared to the male population (42.4% versus 40.4%), as shown in figure 4.2. This is similar to previous findings in Nigerian hypertensive subjects (Kolo PM et al 2008, Karaye KM et al 2008). Gender-specific differences in left ventricular geometric pattern have recently been demonstrated by Rider et al. in obese subjects, who found that obese men have predominantly concentric hypertrophy, whereas obese women exhibit both eccentric and concentric hypertrophy (Rider OJ et al 2013). The higher prevalence of concentric LVH,

compared to other geometric patterns, is an important finding as the prevalence of death and cardiovascular complications associated with hypertension is higher in hypertensive patients with concentric hypertrophy than in other groups, including patients with eccentric hypertrophy (Okin PM et al 2002). We found that plasma ST2 levels were increased in hypertensive patients with all three patterns of abnormal LVH geometry, as compared to normal geometry, but highest in those with concentric hypertrophy (Table 4.2) despite comparable blood pressures and left ventricular mass index values. These results suggest that there is not only a relationship between hypertensive LVH and soluble ST2, but that this relationship is in keeping with the particular geometric pattern. Therefore, measurement of soluble ST2 could be useful in detecting the particular geometric abnormalities of LVH, thereby facilitating risk stratification.

More specifically, we found significant correlations between plasma ST2 and left ventricular mass index, inter-ventricular septal wall thickness in diastole, posterior wall thickness in diastole, left ventricular internal diameter in diastole and systole, right atrial size, left ventricular mass index, left ventricular ejection fraction and transmitral E/A ratio. The correlation of ST2 with left ventricular wall thickness and chamber sizes is a reflection of the mechanism of secretion of ST2 which is related to mechanical stress (Townsend MJ et al 2000). The correlation between left ventricular ejection fraction and transmitral E/A ratio is an indication that serum soluble ST2 levels are not only markers of left ventricular systolic function, but may also be a marker for left ventricular diastolic function in hypertensive heart disease. The correlation with right atrial area (a marker for right ventricular function) implies that serum soluble ST2 may be related to right ventricular function.

We also observed that our hypertensive subjects with concentric hypertrophy had the lowest left ventricular ejection fractions (Table 4.5), compared with those with normal geometry, further supporting the finding that concentric hypertrophy carries the worst prognosis of the geometric patterns in hypertension (Okin PM et al 2002). Lower left ventricular ejection fraction is an independent marker of worse prognosis in hypertensive heart disease (Weir RAP et al 2010). Toshio et al. (Takeda T et al 1995) had earlier reported higher levels of plasma NT-pro BNP, which is another biomarker that correlates well with serum soluble ST 2 in hypertensive subjects with concentric LVH, compared to other geometric patterns. In our study, even though subjects with concentric hypertrophy had the highest concentration of soluble ST2, it was not statistically significant (Table 4.2).

Our findings suggest that the soluble ST2 level is not only affected by ischemic heart disease, but extends to the particular geometric pattern in hypertension. Soluble ST2 may, therefore, be a new method of studying myocardial geometry, not only in ischemic heart disease but in hypertension, and may be a future biomarker for assessing the full impact of hypertension on the myocardium.

5.5 Diagnostic Accuracy of ST2 compared with Electrocardiography in Detecting LVH in Hypertensive Subjects without Heart Failure

Since electrocardiography is the most common means of diagnosing left ventricular hypertrophy and with previous findings that it lacks sensitivity (Levy D et al 1990), we decided to compare the sensitivity of soluble ST2 and ECG in detecting LVH in our one-hundred and thirty-three hypertensive cohorts without heart failure. We found that the diagnostic accuracy of soluble ST2 was greater than that of electrocardiography studies, as evidenced by higher sensitivity and negative predictive value for this marker, as shown in table 4.13. There is the need for this aspect of the study to be carried out in a larger population of hypertensive subjects to validate this point.

5.6 Cardiac Enzymes and Echocardiography in the Assessment of Right Ventricular Function in the Heart Failure Group

Right ventricular function is influenced by both intrinsic factors, such as contraction of the right ventricular myocardium, and by extrinsic factors, such as preload, afterload, left ventricular function, contractile function of the inter-ventricular septum, the pericardium and right coronary artery perfusion (Devereux RB et al 1986,). Furthermore, it has been said that left ventricular failure is the most common cause of right heart failure (Palmieri V et al 1999). Conversely, the right ventricle can influence left ventricular filling through diastolic ventricular interaction (Atherton JJ et al. 1997). This study has shown the influence of hypertensive heart failure on right ventricular function. Although hypertensive heart failure has been previously identified as the most common singular cause of left-sided heart failure (Kizer JR et al 2004, Drazner MH et al 2005, Sharp A et al 2008, Damasceno A et al 2012, Kingue S et al 2005, Commerford P et al 2006, Oyoo GO et al 2006, Amoah AGB et al 1999, Karaye KM et al 2008, Ojji DB et al 2009, Damasceno A et al 2007), the effect on the right ventricle is not well reported. Our study, therefore, is one the first to report the effect of hypertensive heart failure on right ventricular function in the sub-Saharan African population.

We found right ventricular systolic dysfunction in 33 (42.9%) of the seventy-seven (77) subjects that were studied. The high prevalence of right ventricular dysfunction in our hypertensive heart failure cohort might partly explain the poor prognosis that is found in our hypertensive heart failure subjects, as it is a well known fact that right ventricular systolic dysfunction is a poor prognostic factor in heart failure (Jurcut et al 2010, Hines R et al 1986, Dini et al 2012). There is a need, therefore, to pay more attention to right ventricular function which has been previously neglected in our hypertensive heart failure subjects. The affectation of right ventricular function by left heart failure has been linked to ventricular interdependence (Di Salvo TG et al 1995, De Groote P et al 1998). Although ventricular interdependence is always present, it is most apparent with changes in loading conditions, such as those seen with volume loading (Atherton et al. Lancet 1997). Thirty percent of our subjects had tricuspid regurgitation with moderate TR accounting for the highest proportion (18.2%). This was largely functional regurgitation (Stewart S et al 2008) linked to right ventricular dilatation, rather than any structural abnormalities on tricuspid valvular leaflets. The prevalence of tricuspid regurgitation of 30% in our hypertensive heart failure subjects is much higher than that in the Heart of Soweto Study (Stewart S et al 2008). Furthermore, the worse right ventricular function in our subjects, as reflected by higher prevalence of tricuspid regurgitation, may reflect the late presentation of our subjects compared with Soweto, which may be attributed to less access to medical care by our subjects in Abuja compared to Soweto.

Factors found in linear regression analysis to be associated with abnormal RV function are shown in table 4.13 and include dilated left atrium and left ventricle, increased LV mass, reduced LV systolic function, restrictive filling pattern and right ventricular systolic pressure. Dilated left ventricle has been previously shown to have an impact on right ventricular function as measured by TAPSE (Kjaergaard J et al 2007). Also, reduced left ventricular ejection fraction has been shown to have an impact on TAPSE, even in the setting of preserved right ventricular ejection fraction (Di Salvo TG et al 1995, Lopez-Candales A, et al 2006). The effect of left ventricular ejection fraction on TAPSE has been attributed to ventricular interdependence (Di Salvo TG et al 1995, De Groote P, et al 1998). Similar to our findings, TAPSE has been found to be correlated to markers of diastolic dysfunction and right ventricular systolic pressure (Hines R et al 1986), also similar to previous studies, left ventricular end-diastolic diameter were not related to TAPSE (Kjaegaard J et al 2009). Although there was no correlation between TAPSE and serum levels of ST2 and NT-pro BNP in our study, RVSP correlated well with both

serum ST2 and NT-pro BNP with correlation coefficient of 0.75 and 0.54 respectively and p-values of < 0.0001 respectively as shown in table 4.13. This is in keeping with a previous report on heart failure subjects with coronary heart disease as the aetiological factor (Ravi V et al 2009).

At presentation, most of our subjects had chamber dilatation (especially left-sided chambers), which might account for the significant systolic function, with an average left ventricular ejection fraction of 38%. The mean low systolic function in our hypertensive cohort with heart failure is as not surprising systolic function dysfunction has been previously linked to hypertension in the black population. There was also significant and diastolic dysfunction with an average transmitral E/A ratio of 2.2, suggestive of a restrictive filling pattern. Our male subjects had significantly greater chamber dilatation than women. This has already been reported in the Heart of Soweto study (Stewart S et al 2008) and, possibly, linked to genetic factors and higher alcohol consumption in men, compared to women.

Less than 25% of our subjects had heart failure with preserved ejection fraction (LVEF $> 50\%$), lower than what is reported in the western population (30-40%). However, we found HFPEF to be more common in women (55.4%), compared to men (44.6%), which is similar to the Western population (Smith GL et al 2003, Vasan RS et al 1999).

LIMITATIONS

This thesis has a number of limitations. We could have tested for other biomarkers like Cardiotrophin-1 and metalloproteinase but were limited by funds. Also, since the diagnosis of ischaemic heart disease was made clinically using history, electrocardiography and cardiac troponin I with no myocardial perfusion imaging and coronary angiography being performed, it is very possible that subtle coronary artery disease might have been omitted. **However, with the low prevalence of clinical myocardial infarction and the high cost of myocardial perfusion and coronary imaging in this environment we did not think it was justifiable for these subjects to have these investigations.**

In addition, the present thesis is limited by the number of subjects and therefore, the relationship between plasma NT-pro BNP and soluble ST2 should be largely viewed as hypothesis-generating for studies in population group. This report involved a relatively small sample sizes and also groups with unequal numbers. In order to assess the predictive power of these markers and generate more accurate conclusions as regards

how they relate to the different spectrum of hypertensive heart disease, a larger prospective study involving serial biomarker assessment in a large number of subjects should be carried out.

In spite of these limitations enumerated above, the careful and extensive phenotyping of our study subjects as regards clinical, echocardiographic and biochemical parameters is a strong point for this thesis.

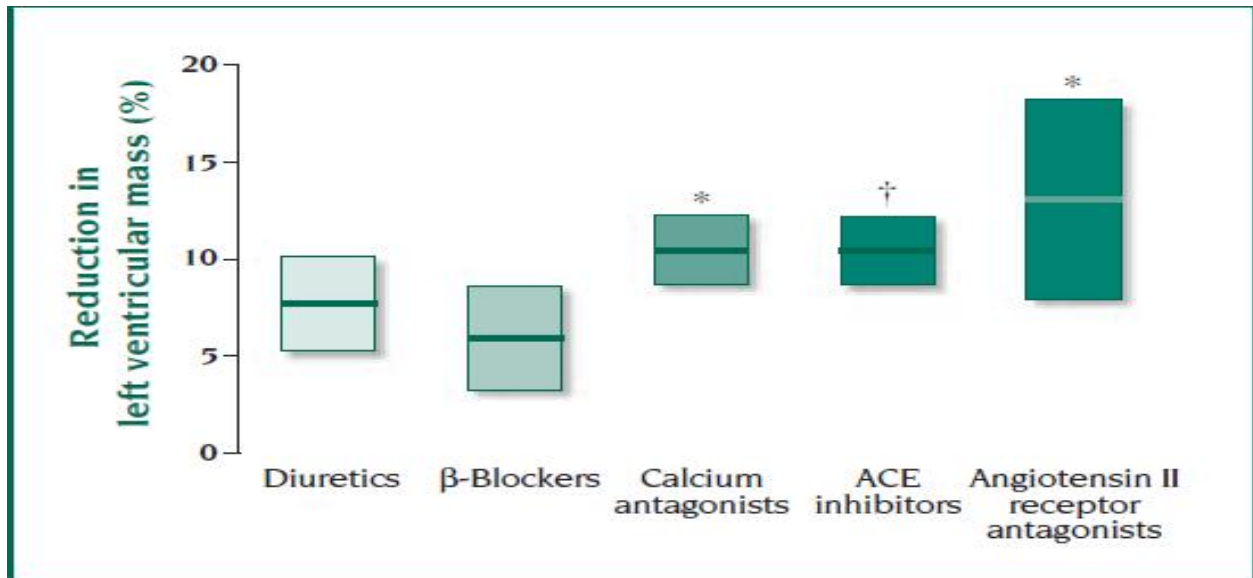


Figure 5.1: Meta-analysis of the efficacy of different antihypertensive drug classes in decreasing left ventricular mass =P<0.05 versus β-blocker, †= P<0.01 versus β-blocker (adapted from Klingbeil et al 2003)

CHAPTER 6

CONCLUSION AND PERSPECTIVES

This PhD thesis has contributed considerably in showing that soluble ST2 has a high sensitivity and specificity in detecting and differentiating the various spectrum of ventricular remodelling in hypertensive heart disease. We have also shown that soluble ST2 does not only complement the role of NT-pro BNP in differentiating the different spectrum of hypertension but is a better biomarker than NT-pro BNP in this regard (Figure 6.1). Our findings will therefore assist in identifying patients at higher risk of evolution to heart failure and thereby halting this process by initiating appropriate medications which will include the rennin-angiotensin-aldosterone blockers, and close follow-up and monitoring of such patients. As it is well known that LVH if untreated often progresses to heart failure in more than 50% of cases (Drazner et al 2005), early diagnosis of hypertensive LVH and appropriate treatment using medications like angiotensin converting enzyme inhibitors and angiotensin receptor blockers has the potential to reduce and delay the onset of hypertensive heart failure. This will therefore in no small reduce the burden of hypertensive heart failure which is the commonest form of heart failure in our environment (Damasceno et al 2012).

Soluble ST2 concentration was also found not only to be higher in hypertensive subjects with left ventricular hypertrophy when compared with those without hypertrophy, but was further highest in concentric hypertrophy compared to other geometric patterns. This is also very important finding as the extent of the risk posed by left ventricular hypertrophy in hypertension also depends on the particular geometric pattern, with concentric LVH having a higher prevalence of associated cardiovascular complications or death than those with other geometric patterns. In addition, subjects with concentric LVH also have also been found to have the most advanced extra-cardiac target-organ damage compared to other geometric pattern. As increasing evidence has demonstrated the central importance of left ventricular mass and geometry especially concentric hypertrophy in the pathophysiology and prognosis of hypertension, early identification of these measures of preclinical disease as shown in our study with soluble ST2 can aid clinical decision- making by separating patients into those with a high or a relatively low risk with the need for pharmacological treatment with medications containing the rennin-angiotensin-aldosterone system blockers or its intensification in those at high risk.

Apart from the association of soluble ST2 with left-sided chamber sizes, the concentration of soluble ST2 also correlated well with right atrial area and right ventricular diameter much more than NT-pro BNP. Therefore, soluble ST2 and NT-pro BNP are not only markers of left cardiac chamber remodelling but may have place on the remodelling of the right cardiac chambers. And this may therefore be a pointer to the importance of right ventricular remodelling in hypertensive heart disease which has been previously neglected. In addition, we found that a large proportion of our subjects (42.9%) with hypertensive heart failure of the showing further that right ventricular function assessment is important in the assessment of the hypertensive subject with heart failure.

Also, this thesis contributes to our knowledge of the role of NT-pro BNP in cardiac remodelling in hypertension in African subjects. Most especially, this is one of the first works that has shown that the role of NT-pro BNP in hypertension although weakly, transcends left ventricular remodelling to the remodelling of the right ventricle. Furthermore, the present thesis has shown that the, soluble ST2 is not only a marker in the diagnosis of ischaemic heart disease, but it is very important in the diagnosis of the various spectrum of hypertensive heart disease and in identifying hypertensive concentric hypertrophy. Soluble ST2 may therefore be a new method of studying myocardial geometry in not only ischemic heart disease but in hypertension, and may be a future biomarker in assessing the full impact of hypertension on the myocardium. This thesis has therefore created the need for soluble ST2 to be tested in a larger prospective study involving a larger number of patient and also a longitudinal study to investigate if its role extends beyond diagnosis to therapeutic monitoring with the ultimate aim of developing a point-of-care which will eventually guide in the choice of medications like angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-1-selective agents and long-acting calcium antagonists, and also lifestyle changes which have been proven to regress LVH. For example, the beta-1-selective blockers, Bisoprolol and Atenolol were shown to cause regression of LVH in hypertensive subjects (Gosse P et al 1990, Margaroli et al 1985), just like Metoprolol (Cifkova R, et al 1987). The long acting calcium channel blocker was also found to cause LVH regression in hypertensive diabetic subjects (Nalbantgil et al 1996). In addition, numerous investigations have demonstrated the beneficial effect of angiotensin converting enzyme inhibitors on LVH regression such as Captopril (Lombardoi M et al 1983), Fosinopril (Cheung BMY et al 1999) and lisinopril (Shimamoto H et al 1996, Rizzoni et al

1997). Furthermore, several angiotensin receptor blockers like Losartan (Cuspidi et al 1998) and Candesartan (Mitsunami K et al 1998) have been shown to cause regression of LVH in hypertensive patients. Apart from the use of therapeutic agents, the TOMHS-Study showed that appropriate lifestyle changes in antihypertensive treatment causes significant regression of LVH in patients with mild hypertension (Liebson et al 1995). **Another possible area of the use of this novel biomarker is the monitoring of the effectiveness of such therapeutic agents like angiotensin converting enzyme inhibitors and angiotensin receptor blockers in the regression of LVH in hypertensive heart disease. To determine this, a follow up study of a cohort of hypertensive disease subjects will be needed.**

However, for such an assay to be used as point of care it must be cheaper and easier to perform compared to conventional electrocardiography and echocardiography. For example, the present cost of assaying for NT-Pro BNP in private health facilities in Abuja, Nigeria which is three to four times above that of electrocardiography and comparable with that of echocardiography restricts its use in clinical practice.

Also of note, the present thesis is one of the first studies in sub-Saharan Africa to show that a large proportion of our hypertensive heart failure subjects have right ventricular systolic dysfunction on presentation, further strengthening the need for the full assessment of right ventricular systolic to be part of echocardiography protocol in our hypertensive heart failure subjects.

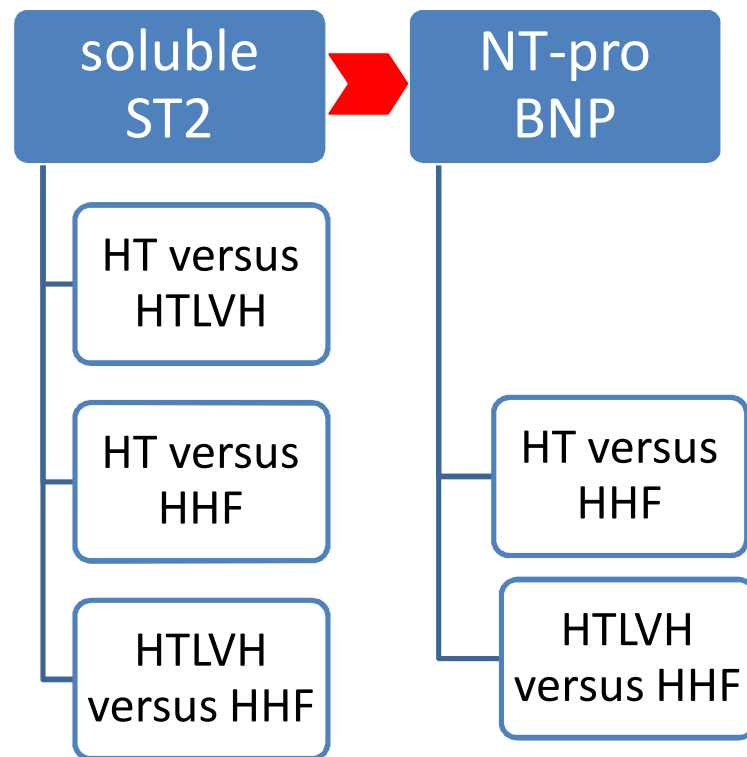


Figure 6.1: Schematic diagram comparing soluble ST2 and NT-Pro BNP as Biomarkers in Hypertensive Heart Disease. HT= Hypertension without LVH and heart failure, HTLVH= Hypertension with LVH but no heart failure, HHF=Hypertensive Heart Failure.

 =Better than.

INVESTIGATION	COST	SENSITIVITY	ACCESSIBILITY	PRACTICALITY (NEED FOR TRAINING)
ECHOCARDIOGRAPHY	+++	+++	-	-
ECG	-	-	+	++
NT-PRO BNP	++	+	+	+

ST2	++	++	+	+
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Figure 6.1 Comparison of different markers for ventricular remodelling in hypertensive patients. Our study demonstrates that, unlike NT-pro BNP, soluble ST2 differentiates the whole spectrum of hypertensive heart disease. The relative lower cost, the absence of special training and the better accessibility of ST2 analysis compared to echocardiography suggests that ST2 analysis should be implemented as a routine test in patients with hypertensive disease, especially in countries where access to echocardiography is difficult.

PUBLICATIONS RELATED TO THIS WORK AND PREVIOUS PUBLICATIONS ON HYPERTENSION, HEART FAILURE AND LEFT VENTRICULAR GEOMETRY

1. The Relationship between Left Ventricular Geometry and Soluble ST2 in a Cohort of Hypertensive Subjects. **Ojji DB**, Opie LH, Lecour S, Lacerda L, Adeyemi O, Sliwa K. *Accepted Journal Clinical Hypertension. August 2013.*
2. The Effect of Left Ventricular Remodelling on Soluble ST2 in a Cohort of Hypertensive Subjects **Ojji Dike B**, MD, Opie Lionel H, Lecour Sandrine, PHD, Lacerda Lydia PHD², Adeyemi Olusoji M, Sliwa Karen. *Under Review Journal Hum Hypertension.*
3. A predominance of hypertensive heart failure in the Abuja Heart Study cohort of urban Nigerians: a prospective clinical registry of 1515 de novo cases. **Ojji D**, Stewart S, Ajayi S, Manmak M, Sliwa K. *Eur J Heart Fail.* 2013 Aug; 15 (8):835-842.
4. The Causes, Treatment, and Outcome of Acute Heart Failure in 1006 Africans from 9 Countries: Results of the Sub-Saharan Africa Survey of Heart Failure. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, **Ojji D**, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. *Arch Intern Med.* 2012 Oct 8; 172(18):1386-1394.
5. Pattern of Prescription of Anti-Hypertensive Medications in a Tertiary Health Care Facility in Abuja, Nigeria. **Ojji Dike B**, Ajayi Samuel O, Mamven Manmak H , Alfa Jacob, Albertino Damasceno. *Accepted Ethnicity and Disease* May 2013.
6. Prevalence of metabolic syndrome among hypertensive patients in Abuja, Nigeria. **Ojji DB**, Ajayi SO, Mamven MH, Alabi P. *Ethn Dis.* 2012 Winter; 22 (1):1-4
7. Pattern of heart failure in Abuja, Nigeria: an echocardiographic study. **Ojji DB**, Alfa J, Ajayi SO, Mamven MH, Falase AO. *Cardiovasc J Afr.* 2009 Nov-Dec; 20(6):349-52.

8. Characterisation of heart failure with normal ejection fraction in a tertiary hospital in Nigeria. Adebayo AK, Adebayo AA, Oladapo OO, Ogah OS, Aje A, **Ojji DB**, Falase AO. BMC Cardiovasc Disord. 2009 Nov 18; 9:52.
9. Blood pressure control and left ventricular hypertrophy in hypertensive Nigerians. Salako BL, Ogah OS, Adebisi AA, Oladapo OO, Aje A, Adebayo AK, **Ojji DB**, Ipadeola A, Nwafor CE. Ann Afr Med. 2009 Jul-Sep; 8(3):156-62.
10. Left ventricular geometric patterns in normotensive type 2 diabetic patients in Nigeria: an echocardiographic study. **Ojji DB**, Adebisi AA, Oladapo OO, Adeleye JA, Aje A, Ogah OS, Adebayo AK, Falase AO. Prev Cardiol. 2009 Fall; 12(4).
11. Prevalence of Dyslipidaemia in Newly Presenting Normoglycaemic Hypertensive Subjects in Abuja, Nigeria. **Ojji DB**, Ajayi SO, Mamven MH, Atherton JJ. Journal of Clinical Lipidology (2009) 3:51-56.
12. Characterisation of left ventricular function by tissue Doppler imaging technique in newly diagnosed, untreated hypertensive subjects. Adebayo AK, Oladapo OO, Adebisi AA, Ogunleye OO, Ogah OS, **Ojji DB**, Adeoye MA, Ochulor KC, Enakpene EO, Falase AO. Cardiovasc J Afr. 2008 Sep-Oct; 19(5):259-63.
13. Changes in left atrial dimension and function and left ventricular geometry in newly diagnosed untreated hypertensive subjects. Adebayo AK, Oladapo OO, Adebisi AA, Ogunleye OO, Ogah OS, **Ojji DB**, Aje A, Adeoye MA, Ochulor KC, Enakpene EO, Falase AO. J Cardiovasc Med (Hagerstown). 2008 Jun; 9(6):561-9.
14. Electrocardiographic left ventricular hypertrophy with strain pattern: prevalence, mechanisms and prognostic implications. Ogah OS, Oladapo OO, Adebisi AA, Adebayo AK, Aje A, **Ojji DB**, Salako BL, Falase AO. Cardiovasc J Afr. 2008 Jan-Feb; 19(1):39-45.
15. Echocardiographic partition values and prevalence of left ventricular hypertrophy in hypertensive Nigerians. Adebisi AA, Ogah OS, Aje A, **Ojji DB**, Adebayo AK, Oladapo OO, Falase AO. BMC Med Imaging. 2006 Aug 29; 6:10.
16. Association between electrocardiographic left ventricular hypertrophy with strain pattern and left ventricular structure and function. Ogah OS, Adebisi AA, Oladapo OO, Aje A, **Ojji DB**, Adebayo AK, Salako BL, Falase AO. Cardiology. 2006; 106(1):14-21.

17. Left ventricular geometric patterns in newly presenting Nigerian hypertensives: an echocardiographic study. Aje A, Adebisi AA, Oladapo OO, Dada A, Ogah OS, **Ojji DB**, Falase AO. BMC Cardiovasc Disord. 2006 Jan 20; 6:4.
18. Correlates of left atrial size in Nigerian hypertensives. Adebisi AA, Aje A, Ogah OS, **Ojji DB**, Dada A, Oladapo OO, Falase AO. Cardiovasc J S Afr. 2005 May-Jun; 16(3):158-61.
19. Left Ventricular diastolic function parameters in hypertensives. Adebisi AA, Aje A, Ogah OS, **Ojji DB**, Oladapo OO, Falase AO J Natl Med Assoc Jan; 97(1):41-5.

ABSTRACT PROCEEDINGS

1. Markers of left and right ventricular remodelling in a native African hypertensive cohort. Dike B. Ojji, Lydia Lacerda, Sandrine Lecour, Olusoji Adeyemi -BillyRose, Karen Sliwa. Circulation 2012, 125(19):p619,
2. Markers of left and right ventricular remodelling in a Nigerian hypertensive cohort
3. Dike Bevis Ojji, Lydia Lacerda, Sandrine Lecour, Matthew Adeyemi Billyrose and Karen Sliwa. Saheart Spring 2011;8(4):251.
4. Spectrum of Hypertension and Hypertension_related Diseases in Abuja, Nigeria. Ojji DB, Ajayi SO, Mamven MH, Sliwa K. CVJA May/June, 22(3):S18.
5. The role of the novel biomarker ST2 as a marker of left ventricular remodelling in a native African Hypertensive Cohort. Saheart Ojji DB, Lecour S, Lacerda L, Adeyemi BM, Sliwa K. CVJA Winter 2012,9(3):188.
6. Markers of left and right ventricular remodelling in a native African Cohort. Ojji D, Lacerda L, Lecour S, Adeyemi BM, Sliwa K. Pulmonary Vascular Research Institute 5th Scientific Workshops and Debates. Cape Town, 2012.
7. The Complementary Roles of the Novel Biomarker ST2 and NT-Pro BNP in African Hypertensive Subjects. Ojji DB, Opie LH, Lecour S, Lacerda L, Adeyemi BM, Sliwa K. CVJA 2013 Jan/Feb 24(1):289.
8. Soluble ST2 detects Left Ventricular Geometric Patterns in a Cohort of African Hypertensive Subjects Ojji DB, Opie LH, Lecour S, Lacerda L, Adeyemi BM, Sliwa K. CVJA May 2013;24(5):24.
9. The Spectrum of Heart Disease in Two Cities in sub-Saharan Africa Undergoing Socio-Economic Transition. Ojji D, Stewart S, Ajayi S, Mamven M, Alfa A, Sliwa K. CVJA May 2013; 24(5): 24.

10. The role of the novel biomarker ST2 as a Marker of left ventricular remodelling in a native African Hypertensive Cohort Ojji D, Lacerda L, Lecour S, Adeyemi Billyrose M Sliwa K. 2nd UK-SA Cardiovascular Research Work Shop. Cape Town, South Africa. August 2013.
11. Soluble ST2 differentiates Hypertensives with or without Left Ventricular Hypertrophy from those with Heart Failure. Ojji DB, Opie LH, Lecour S, Lacerda L, Adeyemi BM , Sliwa K. European Heart Failure Congress, Lisbon, Portugal, 2013. P785.
12. Soluble ST2 detects Left Ventricular Geometric Patterns in a Cohort of African Hypertensive Subjects. Ojji DB, Opie LH, Lecour S, Lacerda L, Adeyemi BM, Sliwa K. European Society of Cardiology Congress. Accepted Poster.

TRAINING AND WORKSHOPS RELEVANT TO PHD

1. SAHA-Based Mayo Clinic Group (Sun City). Echocardiography Workshop 2010.
2. PASCAR (Uganda). Echocardiography Workshop. May 2011
3. The University of Chicago USA NIH-Based Clinical Center Course on the Principles and Practice of Clinical Research. Abuja, Nigeria. 2011
4. 2nd UK-SA Cardiovascular Research Workshop. Cape Town 2013

REFERENCES

1. Amoah AGB, Kallen C. Aetiology of Heart Failure as seen from a National Cardiac Referral Centre in Ghana. *Cardiology* 2000; 93:1-2.
2. Addo J, Smeeth L, Leon DA. Hypertension in sub-Saharan Africa: a systematic review. *Hypertension* 2007; 50:1-7.
3. Ahmed SH, Clark LL, Pennington WR, Wbb CS, Bonnema DD, Leonardi AH, McClure CD, Spinale FG, Zile MR. Matrix metalloproteinase/tissue inhibitors of metalloproteinase: relationship between changes in proteolytic determinants of matrix composition and structural, functional and clinical manifestations of hypertensive heart disease. *Circulation* 2006; 113(17): 2089-2096.
4. Aje A, Adebisi AA, Oladapo OO, Dada A, Ogah OS, Oji DB, Falase AO. Left ventricular geometric patterns in newly presenting Nigerian hypertensives: An echocardiographic study. *BMC Cardiovasc Disorders*. 2006; 6:4.
5. Akhter SA, Luttrell LM, Rockman HA, Iaccarino G, Leftlowitz RJ, Koch WJ. Targeting the receptor . Gq interface to inhibit in vivo pressure overload myocardial hypertrophy. *Science* 1998; 280(5363): 574-577).
6. Akinkugbe OO. Non-communicable diseases in Nigeria . Final report of a national survey. Federal Ministry of Health - National Expert Committee on Non-communicable Diseases. 1997; 1-12.
7. Aje A, Adebisi AA, Falase AO. Hypertensive heart disease in Africa. *SA Heart* 2009; 6(1): 42 . 51.
8. Andence AD, Katibi IA. Correlation between left ventricular mass and electrocardiographic variables among hypertensive Nigerians. *Niger J Med* 2001; 10(4): 182-184).
9. Anthony KK. Pattern of Cardiac Failure in Northern Savanna Nigeria. *Trop Geogr Med* 1980; 32:118-125.
10. Aoki S, Hayakawa M, Ozaki H, Takezako N, Obata H, Ibaraki N, Tsuru T, Tominaga S, Yanagisawa K. ST2 gene expression is proliferation-dependent and its ligand, IL-33, induces inflammatory reaction in endothelial cells. *Mol Cell Biochem* 2010 2010;335:75-81.
11. Arantxa Gonzalez, Begona Lopez, Susana Ravassa, Javier Beaumont, Teresa Arias, Nerea Hermida, Amaia Zudaire and Javier Diez. *Biochemical*

- markers of myocardial remodelling in hypertensive heart disease. *Cardiovascular Research* (2009) 81,509-518.
12. Aronow WS, Ahn C. Association of electrocardiographic left ventricular hypertrophy with the incidence of new congestive heart failure *J Am Geriatr Soc* 1998; 46:1280-1281.
 13. Asai S, Saito Y, Kuwahara K, Mizuno Y, Yoshimura M, Higashikubo C, Tsuji T, Kishimoto I, Harada M, Hamanaka I, Takahashi N, Yasue H, Nakao K. The heart is a source of circulating cardiotrophin-1 in humans. *Biochem Biophys Res Commun* 2000; 279:320-323.
 14. Aurigemma GP, Gottdiener JS, Shemanki L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. *J Am Coll Cardiol* 2001;1042-1048.
 15. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? *J Am Coll Cardiol* 2002; 39:138-141
 16. Bartunek J, Delrue L, van Durme F, Muller O, Casselman F, De Wiest B, Croes R, Verstreken S, Goethals M, deRaedt H, Sarma J, Joseph L, Vanderheyden M. Non myocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. *JACC* 2008; 52(25): 2166-2174.
 17. Bayes-Genis A, Pascual-Figal D, Jannuzi JL, Maisel A, Casas T, Valdes Chavari M, Ordonez-Llanos J. Soluble ST2 monitoring provides additional risk stratification for outpatients with decompensated heart failure. *Rev Esp Cardiol* 2010; 63:1171-1178.
 18. Bella JN, Wachtell K, Palmieri V, Liebson PR, Gerds E, Yitalo A, Koren MJ, Pedersen OL, Rokkedal J, Dahlof B, Roman MJ, Devereux RB. *J Hypertens* 2001 Jan; 19:127-134.
 19. Benetos A, Thomas F, Bean K, Gautier S, Simulyan H, Guize L. Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. *Arch Intern Med* 2002; 162 (5) : 577 . 581).
 20. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med*. 2006; 355:260-269.

21. Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Jannuzzi J, Maisel AS, Fitzgerald RL. Serial Sampling of ST2 predicts 90-day mortality following destabilized heart failure. *J Card Fail* 2008; 9:732-738.
22. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation* 2002; 106:92-99.
23. Bronner LL, Kanter DS, Manson JE. Primary prevention of Stroke. *N Engl J Med* 1995; 333 (21): 1392 . 1400) Wolf PA, Abbot RD, Kannel WB. Atrial fibrillation as an independent risk factor for Stroke: the Framingham Study. *Stroke* 1991; 22(8): 983 . 988.
24. Bouzas-Mosquera A, Brouillon FJ, Alvarez-Garcia N, Peteiro J, Mosquera VX, Castro-Beiras A. *PLos One*. 2012; 7(9):e45570.
25. Buckley MG, Markandu ND, Miller MA, Sagnella GA, MacGregor GA. Plasma concentrations and comparisons of brain and atrial natriuretic peptide in normal subjects and in patients with essential hypertension. *J Hum Hypertens* 1993; 7:245-250.
26. Chahal NS, Lim TK, Jain P, Chambers JC, Kooner JS, Senior R. New insights into the relationship of left ventricular geometry and left ventricular mass with cardiac function: a population study of hypertensive subjects. *Eur Heart J*. 2010; 31: 588-594).
27. Chaturvedi N, Athanassopoulos G, McKeigue PM, Marmot MG, Nihoyannopoulos P. Echocardiographic measures of left ventricular structure and their relation with rest and ambulatory blood pressure in blacks and whites in the United Kingdom. *J Am Coll Cardiol*. 1994, 24: 1499 . 1505.
28. Cheung BMY, Lan CP. Fosinopril reduces left ventricular mass in untreated hypertensive patients: a controlled trial. *Br J Clin Pharmacol* 1999;47:179-187.
29. Chobanian AV, Bakris GL, Black HR, Cushman WK, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report *JAMA*. 2003; 289: 2560).

30. Cifkova R, Niederle P, Romanovska L, Skibova J, Fridi P, Skalicka H, Widimsky J. Heart and vessel hypertrophy in hypertension: Possibilities of regression. *J Hypertens* 1987; 5 (Suppl 5):S407-S410.
31. Commerford P, Mayosi B. An appropriate research agenda for heart failure in Africa. *Lancet* 2006; 367:1884-1886.
32. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R, Luchner A, McDonagh T, Mair J, Nieminen M, Francis G. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003; 24:1710-1718.
33. Cowie MR, Mendez GF. BNP and congestive heart failure. *Prog Cardiovasc Dis* 2002; 44:293-321.
34. Cowie MR, Mendez GF. BNP and congestive heart failure. *Prog Cardiovasc Dis* 2002; 44:293-321.
35. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in primary care. *Lancet* 1997; 350:1349-1353.
36. Criteria Committee, New York Heart Association. Diseases of Heart and Blood Vessels. Nomenclature and Criteria for Diagnosis, 6th edn. Boston: Little, Brown, 1964:114.
37. Cruickshank JK, Beevers DG, Osbourne VL, Haynes RA, Corlett JC, Selby S. Heart attack, stroke, diabetes and hypertension in West Indians, Asians and Whites in Birmingham, England. *Br Med J* 1980;281:1108.
38. Cuspidi C, Lonati L, Sampieri L, Michv I, Macca G, Rocanova JI, Salerno M, Fusi V, Leonettia G. Effects of losartan on blood pressure and left ventricular mass in essential hypertension. *High blood Press* 1998;7:75-79.
39. DeAlonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Grooves BM, Kernis JT. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med* 1991; 115:343-349.
40. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002; 359:995-1003.

41. Damasceno A, Mayosi BM, Sani MU, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. The causes, treatment and outcome of Acute Heart Failure in 1006 Africans from 9 countries. *Arch. Intern Med.* 2012;3:1- 9.
42. Damasceno A, Cotter G, Dzudie A, Sliwa K. Heart Failure in sub-Saharan Africa: Time for Action: *JACC* 2007;17:1688-1693.
43. Daniels LB, Clopton P, Iqbal N, Tran K and Maisel A. Association of ST2 levels with cardiac structure and function and mortality in outpatients. *Am Heart J* 2010; 106:721-728.
44. Dao Q, Krishaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent care setting. *J Am Coll Cardiol* 2001; 37:379-385.
45. Davila DF, Donis JH, Odreman R, Gonzalez M, Landaeta A. Patterns of left ventricular hypertrophy in essential hypertension: should echocardiography guide the pharmacological treatment? *Int J Cardiol.* 2008; 124: 134-138
46. Davlouros PA, Niwa K, Webb G, Gatzoulis MA. The right ventricle in congenital heart disease. *Heart* 2006; 92:i27-i38.
47. De Groote P, Millaire A, Foucher- Hossein C, Nogue O, Marchandise X, Ducloux G, Lablanche JM. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol.* 1998; 32:948-954.
48. De Groote P, Millaire A, Foucher-Hossein C, Nogue O, Marchandise X, Dulcoux G, Lablanche JM. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol* 1998; 32:948-954.
49. De Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JN. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension.* 1994; 23: 600 . 606.
50. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986; 57:450-458.
51. Devereux RB, Casale PN, Eisenberg RR, Miller DH, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy using

- echocardiographic determination of left ventricular mass as the reference standard: Comparison of standard criteria, computer diagnosis and physician interpretation. *J Am Coll Cardiol.* 1984; 3:82-87.
52. Devereux RB, Casale PN, Eisenberg RR, Miller DH, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy using echocardiographic determination of left ventricular mass as the reference standard: comparison of standard criteria, computer diagnosis and physician interpretation. *J Am Coll Cardiol.* 1984;3:82-87.
 53. Devereux RB, de Simone G, Gangu A, Roman MJ. Left ventricular hypertrophy and geometric remodelling in hypertension: stimuli functional consequences and prognostic implications. *J Hypertens Suppl.* 1994; 12: S117. S127.
 54. Devereux RB, James GD, Pickering TG. What is normal blood pressure? Comparism of ambulatory pressure level and variability in patients with normal or abnormal left ventricular geometry. *Am J Hypertens* 1993; 6: 211S-211S.
 55. Devereux RB, Palmieri V, Sharpe N, De Quattro V, Bella JN, de Simone G, Walker JF, Hahn RT, Dahlof B. Effects of once-daily angiotensin-converting enzyme inhibition and calcium channel blockade-based anti-hypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension: the Prospective randomized enalapril study evaluating regression of ventricular enlargement(PRESERVE) trial. *Circulation* 2001; 104:1248-1254.
 56. Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography. Anatomic validation, standardization and comparison to other methods. *Hypertension* 1987; 9:1119-1126.
 57. Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris K, Aurup P, Dahlof B. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004; 292(19): 2350-2356.
 58. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol.* 1995; 25:1143-1153.

59. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure failure. *J Am Coll Cardiol* 1995;25:1143-1153
60. Diamond JA, Phillips RA. Hypertensive heart disease. *Hypertens Res.*2005; 28:191.
61. Dieplinger B, Januzzi J, Steinmair M, Gabriel C, Poelz W, Haltmayer M, Mueller T. Analytical and clinical evaluation of novel high sensitivity assay for measurement of soluble ST2 in human plasma-the Presage ST2 assay. *Clin Chem Acta* 2009; 409:33-40.
62. Dieplinger B, Gegenhuber A, Kaar G, Poelz W, Hatmayer M and Muller T. Prognostic value of established and novel biomarkers in patients with shortness of breath attending an emergency department. *Clin Biochem* 2010; 43:714-719.
63. Dorothea K T, Apostolos I K, Kostass G R, Apostolos ZZ. Brain Natriuretic Peptide. *Hellenic J Cardiol* 2003; 44:266-277.
64. Drazner MH, Dries DL, Peshock RM, Cooper RS, Klassen C, Kazi F, Willett D, Victor RG. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. *Hypertension* 2005; 46:124-129.
65. Drazner MH. The transition from hypertrophy to failure: how certain are we? *Circulation* 2005; 112:936-938.
66. Du Cailar G, Pasquie JL, Ribstein J, Mimran A. Left ventricular adaptation to hypertension and plasma rennin activity. *J Hum Hypertens.*2000; 14: 181 . 188.
67. Dutsan HP, Roccella EJ, Garrison HH. Controlling hypertension. A research success story. *Arch Intern Med.* 1996;156(17):1926-1925.
68. Dzau VJ, Tissue rennin . angiotensin system in Myocardial hypertrophy and failure. *Arch Intern Med* 1993; 153(3): 937-942.
69. Esquitin R, Razzouk L, Peterson GE, Wright JT Jr, Phillips RA, De Backer TL, Baran DA, Kendrick C, Greene T, Reiffel J, Muntner P, Farkouh ME. Left ventricular hypertrophy by electrocardiography and echocardiography in the African American Study of Kidney Disease Cohort Study. *J Am Soc Hypertens.*2012; 6:193-200.

70. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; 360: 1347 . 1360).
71. Ezzati M, Vander Hoorn S, Lawes CM, Leach R, James WP, Lopez AD, Rodgers A, Murray. Rethinking the diseases of affluence paradigm: global patterns of nutritional risks in relation to economic development. *PLoS Med* 2005; 2:e133.
72. Fagard RH, Staessen JA, Thijs L. Prediction of Cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* 1997; 29: 22-29.
73. Field ME, Solomon SD, Lewis EF, Kramer DB, Baughman KL, Stevenson LW, Tedrow UB. Right ventricular dysfunction and adverse outcome in patients with advanced heart failure. *J Card Fail.* 2006;12:616-620.
74. Foppa M, Duncan BB, Rohde LE. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy. *Cadiovasc Ultrasound* 2005; 3:17.
75. Fruhwald FM, Fahrleitner A, Watzinger N, Fruhwald S, Dobnig H, Schumacher M, Maier R, Zweiker R, Klein WW. Natriuretic peptides in patients with diastolic dysfunction due to idiopathic dilated cardiomyopathy. *Eur Heart J* 1999; 20:1415-1423.
76. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JH. Patterns of left ventricular hypertrophy and geometric remodelling in essential hypertension. *J Am Coll Cardiol* 1992; 19: 1550-1558.
77. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JN, Patterns of left ventricular hypertrophy and geometric remodelling in essential hypertension. *J Am Coll Cardiol* 1992; 19: 1550-1558.
78. Ganau A. Devereux RB, Pickering TG, Roman MJ, Schnall PL, Santucci S, Spitzer MC, Laragh JH. Relation of left ventricular hemodynamic load and contractile performance to left ventricular mass in hypertension. *Circulation* 1990; 81:25-36.
79. Gardin JM, Arnold AM, Bild DE, Smith VE, Lima JA, Klopfenstein HS, Kitzman DW. Left ventricular diastolic filling in the elderly: the cardiovascular health study. *Am J Cardiol* 1998; 82:345-351.

80. Gardin JM, WagenKneht LE, Anton-Culver H, Flack J, Gidding S, Kurosaki T, Wong ND, Manolio TA. Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women. The CARDIA Study. *Circulation* 1995; 92: 380-387.
81. Gavazzi A, Berzuini C, Campana C, Inserra C, Ponzetta M, Sabastiani R, Ghio S, Recusani F. Value of right ventricular ejection fraction in predicting short-term prognosis of patients with severe chronic heart failure. *J Heart Lung Transplant*. 1997; 16:774-785.
82. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001; 37:183-18.
83. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol* 2001; 37:183-188.
84. Giuseppe Schillaci, Leonella Pasqualini, Paolo Verdecchia, Gaetano Vaudo, Simona Marchessi, Carlo Porcellati, Giovanni de Simone, Elmo Mannarino. Prognostic Significance of Left Ventricular Diastolic Dysfunction in Essential Hypertension. *JACC* 2002; 39(12):2002-2011.
85. Goldberg RJ, Ciampa J, Lessard D, Meyer TE, Spencer FA. Long-term survival after heart failure: a contemporary population-based perspective. *Arch intern Med* 2007; 167:490-496.
86. Gonzalez A, Lopez B, Martin-Raymond Lozano E, Varo N, Barba J, Serrano M, Diez J. Usefulness of plasma cardiotrophin-1 in assessment of left ventricular hypertrophy regression in hypertensive patients. *J Hypertens* 2005; 23:2297-2304.
87. Gonzalez A, Ravassa A, Loperena I, Lopez b, Beaumont J, Querejeta R, Larmen M, Diez J. Association of depressed cardiac gp 130-mediated antiapoptotic pathways with stimulated cardiomyocyte apoptosis in hypertensive patients with heart failure. *J Hypertens* 2007; 25:2148-2157.
88. Gosse P, Roudant R, Herrero G, Dallochio M. b-Blockers vs angiotensin converting inhibitors in hypertension: effects on left ventricular hypertrophy. *J Cardiovasc Pharmacol* 1990; 16(Suppl 5): S145-S150.

89. Gott diener JS, Reda DJ, Materson BJ, Massie BM, Notargiacomo A, Hamburger RJ, Williams DW, Henderson WG; the department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Importance of Obesity, race and age to the cardiac structural and functional effects of hypertension. *J Am Coll Cardiol*. 1994; 24:1492-1498.
90. Gupta S, Khan F, Shapiro M, Weeks SG, Litwin SE, Michaels AD: The associations between tricuspid annular plane systolic excursion (TAPSE), ventricular dyssnchrony and ventricular interaction in heart failure patients. *Eur J Echocardiogr* 2008, 9:766-771.
91. Hammond IW, Alderman MH, Devereux RB, Luts EM, Laragh JH. Contrast in cardiac anatomy and function between black and white patients with hypertension. *J Nat Med Assoc*. 1984; 76: 247 . 255.
92. Harrap SB, Dominiczak AF, Frazer R, Lever AF, Morton JJ, Foy CJ, Watt GC. Plasma angiotensin II, predisposition to hypertension and left ventricular size in healthy young adults. *Circulation* 1996; 93(6) 1148 . 1154).
93. Harrington M, Kincaid. Smith P, Mc Micheal J. Results of treatment in malignant hypertension: a seven . year experience in 94 cases. *BMJ* 1959: 2: 969 . 980).
94. Hart CYT, Redfield MM. Diastolic heart failure in the community. *Curr Cardiol Rep* 2000; 2:461-469).
95. Hasegawa K, Fujiwara H, Doyama K, Miyamae M, Fujiwara T, Suga S, Mukoyama M, Nakao K, Imura H, Sasayama S. Ventricular expression of brain wnatiuretic peptide in hypertrophic cardiomyopathy. *Circulation* 1993; 88:372-80.
96. He J. Whelton Pk. Epidemiology and prevention of hypertension. *Med Clin North Am* 1997, 81:1077 . 1097.
97. Whelton Pk. Epidemiology of hypertension. *Lancet* 1994; 344:101 . 106.
98. Hinderliter AL, Light KC, Willis PWT. Racial differences in left ventricular structure in healthy young adults. *Am J Cardiol* 1992; 69 (14): 196 . 199.
99. Hines R, Barash PG. Intra-operative right ventricular dysfunction detected with a right ventricular ejection fraction catheter. *J Clin Monit* 1986; 2: 206-208.
100. Hines R. Right ventricular function and failure: a review. *Yale J Biol Med* 1991; 64: 295-307.

101. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high-risk community populations. *Br Med J* 2002; 324:1498-1500.
102. Hogg K, Swedberg K, Mc Murray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*. 2004; 43:317-319.
103. Hunt PJ, Espiner EA, Nicholls MG, Richards AM, Yandle TG. The role of the circulation in processing pro-brain natriuretic peptide (proBNP) to amino-terminal BNP and BNP-32 Peptides 1997; 18:1475-1481.
104. Imamura T, Mc Dermot PJ, Kent RL, Nagatsu M, Cooper G, Carabello BA. Acute changes in myosin heavy chain synthesis rate in pressure versus volume overload. *Circ Res* 1994; 75(3): 418-425.
105. Ishikawa M, Saito Y, Kuwahara K, Ogawa E, Nakagawa O, Harada M, Masuda I, Nakao K. CDNA cloning of cardiotrophin-1 (CT-1): augmented expression of CT-1 gene in ventricle of genetically hypertensive rats. *Biochem Biophys Res Commun* 1996;219:377-381.
106. Ishikawa M, Saito Y, Miyamoto Y, Harada M, Kuwahara K, Ogawa E, Nakagawa O, Hamanaka I, Kajiyama N, Takahashi N, Masuda I, Hashimoto T, Sakai O, Hosoya T, Nakao K. A heart-specific increase in cardiotrophin-1 gene precedes the establishment of ventricular hypertrophy in genetically hypertensive rats. *J Hypertens* 1999;6:807-816.
107. Januzzi JL, Peacock WF, Maisel AS, Chae CU, Jesse RL, Baggish AL, O'Donoghue M, Sakhyia R, Chen AA, van Kimmenade RR, Lewandrowski KB, Lloyd-Jones DM, Wu AH. Measurements of the interleukin family member ST2 in patients with acute dyspnoea: results from the PRIDE (pro-brain natriuretic peptide investigation of dyspnoea in the emergency department) study. *J Am Coll Cardiol* 2007;50:607-613.
108. Kjaegaard J, Iversen KK, Akkan D, Moller JD, Kober LV, Torp-Pedersen C, Hassager C. Predictors of right ventricular function as measured by tricuspid annular plane systolic excursion in heart failure. *Cardiovascular ultrasound*. 2009;7:51.
109. Juilliere Y, Barbier G, Feldmann L, Grentzinger A, Danchin N, Cherrier F. Additional predictive value of both left and right ventricular ejection

- fractions on long-term survival in idiopathic dilated cardiomyopathy. *Eur Heart J* 1997; 18: 276-280.
110. Jurcut R, Giusca S, La Gerche A, Vasile S, Ginhina C, Voigt JU. The echocardiographic assessment of the right ventricle: what to do in 2010? *Eur J Echocardiogr.* 2010 Mar;11(2):81-96.
 111. Kakkar R, Lee RT. The IL-33/ST 2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov.* 2008;7:827-840.
 112. Karaye KM and Sani MU. Factors associated with poor prognosis among patients admitted with heart failure in a Nigerian tertiary medical centre: a cross-sectional study. *BMC Cardiovascular Disorder* 2008; 8:16.
 113. Kannel WB, Wilson Houghton JL, Smith VE, Strogatz DS, Henches NL, Breisblatt WM, Carr AA. Effect of African . American race and hypertensive left ventricular hypertrophy, coronary vascular reactivity and endothelial function. *Hypertension* 1997; 29: 706-714.
 114. Kannel WB, Wilson PWF. Cardiovascular risk factors and hypertension. In: 1220 JL Jr, Black HR, editors. *Hypertension primer*. 3rd edition. Dallas (Tx): American Heart Association; 2003. P. 235-238.
 115. Karaye KM, Sani MU. Factors associated with poor prognosis among patients admitted with heart failure in a Nigerian tertiary medical centre: a cross-sectional study. *BMC Cardiovasc Disorders.* 2008;22:16.
 116. Sliwa K, Lee GA, Carrington MJ, Obel P, kreglicki A, Stewart S. *Int J Cardiol* 2012;doc:10.1016/j.ijcard.2012.06.005.
 117. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense H, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodriguez-Artelago F, Stegmatyr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F. Hypertension prevalence and Blood pressure levels in 6 European countries, Canada, and the united States. *JAMA* 2003; 289 (18): 2363 . 2369.
 118. Khouri MG, Peshock RM, Ayers CR, de Lemos JA, Drazner MH. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry. The Dallas Heart Study . *Circ Cardiovasc Imaging* 2010 Mar; 3(2):164-171.
 119. Kingue S, Dzudie A, Menanga A, Akono M, Ouankou M, Muna W. A new look at the adult chronic heart failure in Africa in the age of Doppler echocardiography: experience of the Medicine Department at the Yaounde

- General Hospital (in French). *Ann Cardiol Angeiol (Paris)* 2005; 54: 276. 283.
120. Kinque S, Dzudie A, Menanga A, Akono M, Quankou M, Muna WA. A new look at adult chronic heart failure in Africa in the age of Doppler echocardiography: experience of the Medicine Department at Younde General Hospital (In French). *Ann Cardiol Angeiol (Pans)* 2005; 54: 276 . 28363.
 121. Kizer JR, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Devereux RB. Differences in left ventricular structure between black and white hypertensive adults. The Hypertension Genetic Epidemiology Network Study. *Hypertension* 2004; 43: 1182-1188.
 122. Kizer JR, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Devereux RB. Differences in left ventricular structure between black and white hypertensive adults: the Hypertension Genetic Epidemiology Network Study. *Hypertension*. 2004; 43:1182-1188.
 123. Kjaergaard J, Akkan D, Iversen KK, Kober L, Torp-Pedersen C, Hassager C: Right ventricular dysfunction as an independent predictor of short and long-term mortality in patients with heart failure. *Eur J Heart Fail* 2007; 9:610-616
 124. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, et al. Blood pressure and end-stage renal disease in men. *New Engl J Med* 1996; 334 (1): 13-18.
 125. Klingbeli AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 115(1):41-46.
 126. Kohno M, Horio T, Yokokawa K, Murakawa K, Yasunari K, Akioka K, Tahara A, Toda I, Takeuchi K, Kurihara N. Brain natriuretic peptide as a cardiac hormone in essential hypertension. *Am J Med* 1992; 92:29-34.
 127. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 14(5): 345-352.

128. Koren MJ, Mensah GA, Blake J, Laragh JH, Devereux RB. Comparison of left ventricular mass geometry in black and white patients with essential hypertension. *Am J Hypertens* 1993; 6: 815 . 823.
129. Kruger S, Graf J, Kunz D, Stickel T, Hanrath P, Janssens U. Brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. *Am Coll Cardiol* 2002; 40:718-722.
130. Krumholz HM, Larson M, Levy D. Sex Differences in cardiac adaptation to isolated systolic hypertension *Am J Cardiol.* 1993; 72: 310-313.
131. Kuwahara K, Saito Y, Harada M, Ishikawa M, Ogawa E, Miyamoto Y et al. Involvement of cardiotrophin-1 in cardiac myocyte-nonmyocyte interactions during hypertrophy of rat cardiac myocytes in vitro. *Circulation* 1991;100:1116-1124.
132. La Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultraendurance exercise. *Heart* 2008; 94:860-866.
133. Lavie CJ, Milani RV, Ventura HO, Messerli FH. Left ventricular geometry *AM J Cardiol* 2006; 98(10):1396-1399.
134. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. *Ann Intern Med* 1988; 108: 7-13.
135. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP, Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. *Ann Intern Med* 1998; 108:7-13.
136. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in Framingham Heart Study. *N Engl J Med* 1990; 322: 1561-1566.
137. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. *Ann Intern Med* 1989; 110:101-107.
138. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in Framingham Heart Study. *N Eng J Med* 1990; 322: 1561-1566.

139. Levy D, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelli WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. *Circulation* 1990; 81:815-820.
140. Levy D, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelli WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. *Circulation* 1990; 81:815-820.
141. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557-1562).
142. Lewington S, Clance R, Qizilbash N, Peto R, Collins R. Age specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903 . 1913)/ Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The Sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, Bethesda, Maryland: US Department of Health and Human Services, National High Blood Pressure Education Program. NIH Publication No 98 . 4080, 1997. Izzo JL, Grandman AH. Mechanism and management of hypertensive heart disease: from left ventricular hypertrophy to heart failure *Med. Clin N Am* 2004; 88:1257. 1271.
143. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age . specific relevance of usual blood pressure to vascular mortality: a meta . analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360 (9349): 1903 . 13.
144. Liao Y, Cooper RS, McGee DL, Mensah GA, Ghali JK. The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. *JAMA*. 1995; 273:1592-1597.
145. Lombardo M, Zaini G, Pastori F, Fusco M, Pacini S, Foppoli C. Left ventricular mass and function before and after antihypertensive treatment. *J Hypertens* 1983; 1:215-219.
146. Lopez B, Castello JM, Gonzalez A, Barba J, Diez J. Association of increased plasma cardiotrophin-1 with inappropriate left ventricular mass in essential hypertension. *Hypertension* 2007;50:977-983.
147. Lopez B, Gonzalez A, Lasarte JJ, Sarobe P, Borrás F, Diaz A, Barba J, Tomas L, Lozano E, Serrano M, Varo N, Beloqui O, Fortuno MA, Diez J. Is

- plasma cardiotrophin-1 a marker of hypertensive heart disease? *J Hypertens* 2005;23:625-632.
148. Lopez N, Diez J, Fortuno MA. Differential hypertrophic effects of cardiotrophin-1 on adult cardiomyocytes from normotensive and spontaneously hypertensive rats. *J mol Cell Cardiol* 2006; 41:902-913.
 149. Lopez N, Varo N, Diez J, Fortuno MA. Loss of myocardial LIF receptor in experimental heart failure reduces cardiotrophin-1 cytoprotection. A role for neurohormonal agonists. *Cardiovasc Res* 2007;75:536-545.
 150. Lopez-Candales A, Rajagopalan N, Saxena N, Gulyasy B, Edelman K, Bazaz R: Right ventricular systolic function is not the sole determinant of tricuspid annular motion. *Am J Cardiol* 2006; 98:973-977.
 151. Losartan Intervention For Endpoint. *Am J Hypertens*.2002; 15:663-671
 152. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS. Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction. Comparison with Doppler velocity recordings. *Circulation* 2002; 105:595-601.
 153. Maeda K, Tsutsumota T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998; 135: 825-832.
 154. Maisel A. B-type natriuretic peptide levels: A potential novel ~~white~~ count~~for~~ for congestive heart failure. *J Card Fail* 2001; 7:183-193.
 155. Maisel AS, Koon J, Krishnaswamy P, Kazanegra R, Clopton P, Gardetto N, Morrissey R, Garcia A, Chiu A, De Marca A. Utility of B-natriuretic peptide as a rapid point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. *Am Heart J* 2001;141:367-374.
 156. Mancia G, Zanchetti A, Agabiti . Rosei E, Benemio G, De Casaris R, Fogari R, Pessina A, Porcellati C, Ruppelli A, Salvetti A, Trimarco B. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment . induced regression of left ventricular hypertrophy. SAMPLE Study Group Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation. *Circulation* 1997; 95: 1464 . 1470.
 157. Margaroli P, Petrucci E, Caielli R. Non-invasive assessment of left ventricular anatomy and function in hypertensive patients following

- successful treatment of hypertension with the beta-adrenergic blocking drug atenolol. *Acta Ther* 1985; 11:5-12.
158. Martin M, Stefan J, Erik R, Bjorn Dahlof, Christian H, Olav WN, Anders G, Ronnie W. *Blood Pressure* 2009; 18:196-203.
 159. Martinez-Rumayor A, Carmago CA, Green SM, Baggish AL, O'Donoghue M and Jannuzzi JL. Soluble ST2 plasma concentrations predict 1-year mortality in acutely dyspnoeic emergency department patients with pulmonary disease. *Am J Clin Pathol* 2008; 130:578-584.
 160. Masaki T, Kimura S, Yanagisawa M, Goto K. Molecular and Cellular Mechanism of endothelin regulation. Implications for vascular function. *Circulation* 1991; 84(4) : 1457-1468.
 161. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storror AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly(BNP) Multinational Study. *Circulation* 2002; 106: 416-422.
 162. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Biochemical detection of left ventricular systolic dysfunction. *Lancet* 1998; 351:9-13.
 163. Mensah GA, Barkey NL, Cooper RS. Spectrum of hypertensive target organ damage in Africa: a review of Published Studies. *J Hum Hypertens* 1994; 8 (11): 799 . 808.
 164. Milani RV, Lavie CJ, Mehra MR, Ventura HO, Kutz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. *Am J Cardiol* 2006; 97(7):959-963.
 165. Mildner M, Storka A, Lichtenauer M, Mlitz V, Ghannadan M, Hoetzenecker K, Nickl S, Dome B, Tschachler E, Ankersmit HJ. Primary sources and immunological prerequisites for ST2 secretion in humans. *Cardiovasc Res* 2010; 87:769-777.
 166. Miller AM, Liew FY. The IL-33/ST2 Pathway-A new therapeutic target in cardiovascular disease. *Pharmacol Ther.* 2011; 131:179-186.
 167. Minino AM, Murphy SL, XU JQ, Kochanek KD. Deaths: Final data for 2008. *Natl Vital Stat Rep.* 2011 Dec 7; 59(10):1-126).

168. Mitsunami K, Inoue S, Maeda K. Three-month effects of Candesartan cilexetil an angiotensin II type 1(AT1)-receptor antagonist on left ventricular mass and haemodynamics in patients with essential hypertension. *Cardiovasc Drugs Ther* 1998; 12:469-474.
169. Mocumbi AO, Sliwa K. Women's cardiovascular health in Africa. *Heart* 2012; 98:450-455.
170. Moe GW, Grima EA, Wong NL, Howard RJ, Armstrong PW. Plasma and cardiac tissue atrial and brain natriuretic peptides in experimental heart failure. *J Am Coll Cardiol* 1996; 27:720-727.
171. Mohler ER, Freis ED. Five year survival of patients with malignant hypertension treated with antihypertensive agents. *Human Heart J.* 1960; 60: 329 . 335.
172. Molkenstein JD, Lu JR, Antos CL, Markham B, Richardson J, Robbins J, Grant Sr, Olson EN. A Calcineurin transcriptional pathway for cardiac hypertrophy. *Cell* 1998; 93(2): 215 . 228.
173. Montorsi P, Tonolo G, Polonia J, Hepburn D, Richard M. Correlates of plasma atrial natriuretic factor in health and hypertension. *Hypertension.* 1987;10: 570-576).
174. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. *Circulation* 2007;115:949-952.
175. Moser P, Stanek B, Pacher R. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002; 105:2392-2397.
176. Martinez-Rumayor A, Camargo CA, Green SM, Baggish AL, O'Donoghue M and Jannuzzi JL. Soluble ST2 plasma concentrations predict 1-year mortality in acutely dyspnoeic emergency department patients with pulmonary disease. *Am J Clin Pathol* 2008; 130:578-584.
177. Mueller T, Dieplinger B, Gegenhuber A, Poelz W, Pacher R and Haltmayer M. Increased plasma concentrations of soluble ST2 are predictive for 1-year mortality in patients with acute destabilized heart failure. *Clin chem.* 2008; 54:752-756.
178. Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, Shirakami G, Jougasaki M, Imura H. Human brain natriuretic peptide, a novel cardiac hormone. *Lancet.* 1990; 335:801-804.

179. Muna WF. Cardiovascular disorders in Africa. *World Health Stat Q* 1993; 46: 125-133).
180. Myslinski W, Mosiewicz J, Ryczak E, Barud E, Barud W, Bilan A, Palusinski. Right ventricular function in systemic hypertension. *J Human Hypertens* 1998 Mar;12(3):149-155.
181. Nagaya N, Nishikimi T, Okano Y, Uematsu M, Satoh T, Kyotani S, Kuribayashi S, Hamada S, Kakishita M, Nakanishi N, Takamiya M, Kunieda T, Matsuo H, Kangawa K. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. *J Am Coll Cardiol* 1998; 31:202. 208.
182. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000;102:865. 70.
183. Nakamura S, Naruse M, Naruse K, Kawana M, Nishikawa T, Hosoda S. Atrial natriuretic peptide and brain natriuretic peptide coexist in the secretory granules of human cardiac myocytes. *Am J Hyperetens* 1991;4: 909-912.
184. Nalbantgil I, Oqnder R, Kiliccioglu B, Boydak B, Terzioglu E, Yimaz H. The efficacy of felodipine ER on regression of left ventricular hypertrophy in Advanced hypertensive heart patients with primary hypertension. *Blood Pressure* 1996; 5:285-291.
185. Naruse M, Takeyama Y, Taanabe A, Hiroshige J, Naruse K, Yoshimoto T, Tanaka M, Katagari T, Demura H. Atrial and brain natiuretic peptides in cardiovascular disease. *Hypertension* 1994; 23(suppl I):231-141.
186. Nishigaki K, Tomita M, Kagawa k, Noda T, Minatoguchi S, Oda H, Watanabe S, Morita N, Nakao K, Fujiwara H. Marked expression of plasma brain natiuretic peptide is a special feature of hypertrophic obstructive cardiomyopathy. *J am Coll Cardiol* 1996; 28:1234-1242.
187. Nishikimi T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, Kangawa K, Matsuo H, Matsuoka H. Relationship Between Left Ventricular Geometry and Natriuretic Peptide Levels in Essential Hypertension. *Hypertension* 1996; 28:22-30.
188. Nootens M, Kaufmann E, Rector T, Toher C, Judd D, Francis GS, Rich S. Neurohormonal activation in patients with right ventricular failure from

- pulmonary hypertension: relation to hemodynamic variables and endothelin levels. *J Am Coll Cardiol* 1995; 26:1581. 5.
189. O'Neil L. The Toll/ Interleukin-1 receptor domain: a molecular switch for inflammation and host defence. *Biochem Soc Trans* 2000; 28:557-563.
 190. Ogah OS, Adebajo AT, Otukoya AS and Jagusa TJ. Echocardiography in Nigeria: use, problems, reproducibility and potentials. *Cardiovas Ultrasound* 2006; 4:13.
 191. Ogah OS. Hypertension in Sub. Saharan African populations. The burden of hypertension in Nigeria. *Ethn Dis.* 2006 Autumn, 16(4); 765
 192. Ojji DB, Alfa J, Ajayi SO, Mamven MH, Falase AO. Pattern of heart failure in Abuja, Nigeria: an echocardiographic study. *Cardiovasc J Afr* 2009; 20:349-352.
 193. Ogah OS, Adebajo AT, Otukoya, Jagusa TJ. Echocardiography in Nigeria: use, problems, reproducibility and potentials. *Cardiovascular Ultrasound* 2006; 4:13.
 194. Okin PM, Wright JT, Nieminen MS, Jern S, Taylor AL, Phillipis R, Papademetriou V, Clark LT, Ofili EO, Randall OS, Oikarinen L, Vitasalo M, Toivonen L, Julius S, Dahlof B, Devereux RB. Ethnic differences in electrocardiographic criteria for left ventricular hypertrophy: the Life Study.
 195. Onwuchekwa AC, Asekomah GE. Pattern of heart failure in a Nigerian teaching hospital. *Vascular health and Risk Management* 2009; 5: 745-750.
 196. Ota T, Kisslo J, von Ramm OT, Yoshikawa J. Real-time, volumetric echocardiography: usefulness of volumetric scanning for the assessment of cardiac volume and function. *J Cardiol* 2001, 37(Suppl 1): 93-101.
 197. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Heart Failure with preserved ejection fraction: Trends in prevalence and outcomes. *N Engl J Med.* 2006; 355:251-259.
 198. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis.* 2005; 47:320-332.
 199. Oyoo GO, Ogola EN. Clinical and socio demographic aspects of congestive heart failure patients at Kenyatta National Hospital, Nairobi. *East Afr Med J* 1999; 76:23-27.

200. Oyoo GO, Ogola EN. Clinical and Sociodemographic aspects of congestive heart failure patients at Kenyatta National Hospital, Nairobi. *East Africa Med J* 1999; 76(1): 23. 27.
201. Palmieri V, Bella JN, Arnedt DK, Liu JE, Oberman A, Shuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC, Devereux RB. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) Study. *Circulation* 2001; 103: 102-107.
202. Palmieri V, Dahlof B, DeQuattro V, Sharpe N, Bella JN, de Simone G, Paranicas M, Fishman D, Devereux RB. Reliability of echocardiographic assessment of left ventricular structure and function: the PRESERVE study. Prospective Randomized Study Evaluating Regression of Ventricular Enlargement. *J Am Coll Cardiol* 1999; 34:1625-1632.
203. Parapakham P, Parapakham P, Zimmet H, Billah B, Krum H. B-Type Natriuretic Peptide- Guided Heart Failure Therapy. A Meta-analysis. *Arch Intern Med.* 2010;170(6):507-514.
204. Park SH, Shub C, Nobrega TP, Bailey KR, Seward JB. Two-dimensional echocardiographic calculation of left ventricular mass as recommended by the American Society of Echocardiography: Correlation with autopsy and M-mode echocardiography. *J Am Soc Echocardiogr.* 1996; 9:119-128.
205. Pascual-Figal DA, Ordonez-Llanos J, Tornel PL, Vazquez R, Puig T, Valdes M, Cinca A, de Luna AB, Bayes-Genis A. Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2009; 54:2174-2179.
206. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. *Hypertension* 2000; 36:355-359.
207. Pemberton CJ, Raudsepp SD, Yandle TG, Cameron VA, Richards AM. Plasma cardiotrophin-1 is elevated in human hypertension and stimulated by ventricular stretch. *Cardiovasc Res* 2005;68:109-117.
208. Pennica D, Wood WI, Chien KR. Cardiotrophin-1: a multifunctional cytokine that signals via LIF receptor-gp 130 dependent pathways. *Cytokine Growth Factor Rev* 1996;7:81-91.
209. Perera GA. Hypertensive vascular disease: description and natural history. *J Chron Dis.* 1995; 1: 33-42.

210. Kolo PM, Omotosho ABO, Katibi IA, Sanya EO, Adamu UG, Fasae AJ and Aigbe AF. Gender differences in left ventricular size and geometric patterns of hypertension subjects. *Cardiology* 2008; 4:11-15.
211. Post WS, Hill MN, Dennison CR, Weiss JL, Gerstenblith G, Blumenthal RS. High prevalence of target organ damage in young African American inner city men with hypertension. *J Clin Hypertens* 2003; 5(1): 24 . 30.
212. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RRJ, Januzzi JL. Serum Levels of the Interleukin-1 Receptor Family Member ST2, Cardiac Structure and Function, and Long-Term Mortality in Patients with Acute Dyspnoea. *Circ Heart Fail*.2009; 2:311-319.
213. Rehman SU, Martinez-Rumayor A, Mueller T and Januzzi JL. Independent and incremental prognostic value of multimarker testing in acute dyspnoea: results from the pro BNP Investigation of Dyspnoea in the Emergency Department (PRIDE) study. *Clin Chem Acta* 392:41-45 2008.
214. Reichek N, Devereux RB. Left ventricular hypertrophy: relationship of anatomic echocardiographic and electrocardiographic findings. *Circulation* 1981; 63(6): 1391-1398.
215. Rheeder P, Stolk RP, Mosterd A, Pols HA, Hofman A, Grobbee DE. Insulin resistance syndrome and left ventricular mass in an elderly population (the Rotterdam Study). *Am J Cardiol* 1999; 84: 233-236.
216. Troughton RW, Prior DL, Pereira JL, Martin M, Fogarty A, Morehead A, Yandle TG, Richards AM, Starling RC, Young JB, Thomas JD, Klein AL. Plasma B-type Natriuretic Peptide Levels in Systolic Heart Failure (Importance of Left Ventricular Diastolic Function and Right Ventricular Systolic Function. *J Am Coll Cardiol* 2004;43:416-422.
217. Rizzoni D, Muiesan ML, Porteri E, Piccoli A, Castellano M, Bettoni G, Muiesan ML, Pasini G, Guelfi D, Mulvany MJ, Agabiti Rosei E. Effects of long-term anti-hypertensive treatment with lisinopril on resistance arteries in patients with left ventricular hypertrophy. *Hypertension* 1997; 15:197-204
218. Ross J Jr. On variation in the Cardiac hypertrophic response to pressure overload. *Circulation* 1997; 95: 1349-1351.
219. Talwar S, Siebenhofer A, Williams B, Ng L. Influence of hypertension, left ventricular hypertrophy and left ventricular systolic dysfunction on plasma N terminal pro BNP. *Heart* 2000; 83: 278-282.

220. Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, Rifai N, Cannon CP, Gersten RE, Lee RT. Complementary roles for biomarkers of biochemical; strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. *Circulation* 2008;117: 1936-1944.
221. Sadoshima J, Izumo S. Molecular characterisation of angiotensin II induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. *Circ Res* 1993; 73(3): 413- 42223.
222. European Study Group on Diastolic Heart Failure. Reference values for Doppler indices of left ventricular diastolic filling in the elderly. *Am Soc Echocardiogr* 1993; 6:570-576 European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998; 19:990-1003.
223. Saglam M, Karakaya O, Esen Am, Barutcu I, Dogan S, Karavelioglu Y, Karapinar H, Akgun T, Esen O, Ozdemir N, Turkmen S, Kaymaz C. Contribution of plasma matrix methalloproteinases to development of left ventricular hypertrophy and diastolic dysfunction in hypertensive subjects. *Tohoku J Exp Med* 2006; 208(2): 117-122.
224. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58(60):1072-1083
225. Sakata Y, Yamamoto K, Masuyama T, Mano T, Nishikawa N, Kuzuya T, Miwa T, Hori M. Ventricular production of natriuretic peptides and ventricular structural remodeling in hypertensive heart failure. *Journal of Hypertension* 2001;19:1905-1912.
226. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, Mckenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardio protective signaling system. *J Clin Invest.* 2007; 117:1538-1549.
227. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, Mckenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. *J Clin Invest.* 2007; 117:1538-1549.
228. Sano M, Fukuda K, Kodama H, Takahashi T, Kato T, Hakuno D, Sato T, Manabe T, Tahara S, Ogawa S. Interleukin-6 family of cytokines causes

- angiotensin II-induced delayed STAT 3 activation. *Biochem Biophys Res Commun* 2000;269:798-802.
229. Santamore WP, Dell'Italia LJ: ventricular interdependence: Significant left ventricular contributions to right ventricular systolic function. *Prog Cardiovasc Dis* 1998, 40:289-308.
 230. Santiago G, Muhammed SA, Syed SA, Forum K, Michael YT and Daniel AD. NT-pro BNP has been found as an independent predictor of survival in patients with hypertension and increased left ventricular mass. *Int Journal of Cardiol* 2009; 143(3): 349-52.
 231. Savage DD, Garrison RJ, Kannel WB, Levy D, Anderson SJ, Stokes J III, Feinleib M, Castelli WP: The Spectrum of left ventricular hypertrophy in a general population Sample: the Framingham Study. *Circulation* 1987;75:126-133.
 232. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension. A meta-analysis of randomised double-blind studies. *Jama* 1996; 275(19) :1507-1513.
 233. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR and Jannuzzi JL. Serum levels of interleukin-1 receptor family member ST2 cardiac structure and function and long-term mortality in patients with acute dyspnoea. *Circ Heart Fail* 2009; 2:311-319.
 234. Sharp A, Tapp R, Francis DP, Mc GTSA, Hughes AD, Stanton AV, Zambanini A, Chartuvedi N, Byrd S, Poulter NR, Sever PS, Mayet J. Ethnicity and left ventricular diastolic function in hypertension: an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy. *J Am Coll Cardiol*. 2008; 52:1015-1021.
 235. Shigemitsu Y, Hamada M, Mukai M, Matsuoka H, Sumimoto T, Hiwada K. Clinical evidence for an association between left ventricular geometric adaptation and extracardiac target organ damage in essential hypertension. *J Hypertens*. 1995; 13:155-160.
 236. Shimamoto H, Shimamoto Y. Lisinopril reverses left ventricular hypertrophy through improved aortic compliance. *Hypertension* 1996;28:457-463
 237. Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, Lee RT. Serum levels of the interleukin-1 receptor family member ST2 predicts mortality and clinical outcome in acute myocardial infarction. *Circulation* 2004; 109:2186-2190.

238. Shulman NB, Hall WD. Renal vascular disease in African-Americans and other racial minorities. *Circulation* 1991; 83:1477-1479.
239. Stewart S, Mocumbi AO, Carrington MJ, Pretorius S, Burton R, Sliwa K. A not-so-rare form of heart failure in urban black Africans: pathways to right heart failure in the Heart of Soweto Study cohort. *European Journal of Heart Failure*. 2011; 13:1070-1077.
240. Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, Mc Murray J, Sliwa K. Predominance of Heart Failure in the Heart of Soweto Study Cohort: *Circulation* 2008;118: 2360-2367.
241. Stewart S, Libhaber E, Carrington M, Damasceno A, Abbasi H, Hansen C, Wilkinson D, Sliwa K. The Clinical Consequences and challenges of hypertension in urban-dwelling black Africans: Insights from the Heart of Soweto Study *Int J Cardiol*.2011 Jan;146(1):22-27
242. Sims JE. IL-1 and IL-8 receptors and their extended family. *Curr Opin Immunol*. 2002; 14:117-122.
243. Singh RB, Suh IL, Singh VP, Chaithiraphan S, Laothavorn P, Sy RG, Babilonia NA, Rahman AR, Sheik S, Tomlinson B, Sarraf . Zadisan N. Hypertension and stroke in Asia: Prevalence, control and strategies in developing countries from prevention. *J Hum Hypertens*. 2000; 14: 749 - 763.
244. Sliwa K, Stewart S, Gersh BJ. Hypertension- a global perspective. *Circulation*. 2011;123:2892-2896.
245. Schoen SP, Zimmermann T, Kittner T, Braun MU, Fuhrmann J, Schmeisser A, Strasser RH. NT-pro BNP correlates with right heart haemodynamic parameters and volumes in patients with atrial septal defects. *Eur J Heart Fail* 2007;9:660-666.
246. Staessen JA, Wang WG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta . analysis. *Lancet* 2001; 358 (9290): 1305 . 1315.
247. Ghio S, Tavazzi L. Right ventricular dysfunction in advanced heart failure. *Ital Heart J* 2005; 6(10):852-855.
248. Swnghedauw B. Molecular mechanisms of myocardial remodelling. *Physiol Rev* 1999; 79(1): 215-262.
249. Szerafin T, Brunner M, Horvath A, Szentgyorgyi L, Moser B, Boltz-Nitulescu G, Peterfly A, Hoetzenecker K, Steinleuchner B, Wolner E,

- Ankersmit HJ. Soluble ST2 in Cardiac Surgery: a possible negative feedback loop to prevent uncontrollable inflammatory reactions. *Clin Lab* 2005; 51:657-663.
250. Szerafin T, Niederpold T, Mangold A, Hoetzenecker K, Hacker S, Roth G, Lichtenauer M, Dworschak M, Wolner E, Ankersmit HJ. Secretion of soluble ST2-possible explanation for systemic immunosuppression after heart surgery. *Thorac Cardiovasc Surg* 2009; 57:25-29.
 251. Takeda T and Kohno M. Brain natriuretic peptide in hypertension. *Hypertens Res* 1995; 18:259-266.
 252. Takeda T, kohno M. Brain natriuretic peptide in hypertension. *Hypertension Research* 1995; 18:259-266.
 253. Talwar S, Squire IB, Downie PF, Davies JE, Ng LL. Plasma N-terminal pro-brain natriuretic peptide and cardiotrophin 1 are raised in unstable angina. *Heart* 2000; 84:421-424.
 254. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinants: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976; 37(1):7-11.
 255. The Seventh Report of the Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure. U.S Department of Health and Human Services. NIH Publication August 2004; No 04-5230.
 256. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology: Guidelines for the treatment and diagnosis of chronic heart failure: an executive summary (update 2005). *Eur Heart J* 2005; 26:1115-1140.
 257. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology: Guidelines for the treatment and diagnosis of chronic heart failure: an executive summary (update 2005). *Eur Heart J* 2005; 26:1115-1140.
 258. Weia T, Zenga C, Chena L, Chena Q, Zhaoa R, Lua G, Lua C, Wangb L. Bedside tests of B-type natriuretic peptide in the diagnosis of left ventricular dysfunction in hypertensive patients. *The European Journal of Heart Failure* 2005; 7:75-77.

259. Tonolo G, Richards AM, Manunta P, Troffa C, Pazzola A, Madeddu P. Low doses infusion of atrial natriuretic factor in mild essential hypertension. *Circulation* 1989; 80:893-902.
260. Toshio N, Fumiki Y, Atsushi M, Kazushiko I, Toshihiko I, Yoshihiko S, Kenji K, Hisayuki M, Teruo O, Hiroaki M. Relationship Between Left Ventricular Geometry and Natriuretic Peptide Levels in Essential Hypertension. *Hypertension* 1996;28:22-30.
261. Townsend MJ, Fallon PG, Matthews DJ, Jolin HE, McKenzie AN. T1/ST2-deficient mice demonstrate the importance of T1/ST2 in developing primary T helper cell type 2 response. *J Exp Med* 2000; 191:1069-1076.
262. Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart deaths in England and Wales, 1981 . 2000: company contributions from primary prevention and secondary prevention. *BMJ*.2005; 331:614.
263. Vakili B, Okin P, Devereux RB: Prognostic implications of left ventricular hypertrophy. *Am Heart J*; 2001(141): 334-341.
264. Vakili BA, Okin PM, Devereux RB. Prognostic Significance of left ventricular hypertrophy. *Am Heart J* 2001; 141: 334-341)
265. Van Kimmenade RR, Januzzi JL Jr, Bakker JA, Houben AJ, Rennenberg R, Kroon AA, Crijns HJ, van Dieijen-Visser MP, de Leeuw PW, Pinto YM. *J Am Coll Cardiol* 2009;53:884-890.
266. Vasan RS, Benjamin EJ, Levy D. Prevalence clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 1995; 26:1565-1574.
267. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; 33: 1948-1955.
268. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non- hypertensive participants in the Framingham Heart Study. *Lancet* 2000; 358 :1682 -6
269. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circulation* 2006;113:2335-2362.
270. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR et al. Right ventricular function and figure: Report of a National Heart,

- Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. *Circulation* 2006; 114:1883-1891.
271. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PW, Sutherland P, Omland T, Vasan RS. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002; 90:254-258
 272. Weinberg EO, Shimpo M, Hurwitz, Tominaga S, Rouleau JL, Lee RT. Identification of serum soluble ST2 as a novel heart failure biomarker. *Circulation*. 2003; 107: 721-726.
 273. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, Rouleau JL, Lee RT. Expression and regulation of ST2 , an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation*.2002;106:2961-2966.
 274. Weir RA, Miller AM, Murphy LE, Clemens S, Steedman T, Connell JM, McInnes IB, Dargie HJ, McMurray JJ. Serum Soluble ST2: a potential novel mediator in left ventricular and infarct remodelling after acute myocardial infarction. *J Am Coll Cardiol* 2010; 55:243-250.
 275. Weir RAP, Miller AM, Murphy GEJ, Clements S, Steedman T, Connell JMC, McInnes IB, Dargie HJ, McMurray JJV. Serum Soluble ST2: A Potential Novel Mediator in left Ventricular and Infarct Remodeling After Myocardial Infarction. *JACC* 2010;55:243-250.
 276. Wendelin. Saarehovi M, Isoaho RE, Hartiala JJ, Helenius HY, Kivela SL, Lopponen MK, Puolijoki H, Hietanen EK. Ambulatory blood pressure and left ventricular mass in older age. *Scand J CLin Lab Invest* 2002; 62: 569 . 577.
 277. Woessner JF. Matrix methalloproteinases and their inhibitors in connective tissue remodelling. *Faseb J* 1991; 5(8): 2145-215.
 278. Yamamoto K, Burnett Jr JC, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, Nakao K, Redfield MM. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. *Hypertension* 1996; 28:988-994.
 279. Yandle T, Fischer S, Espiner E, Richards M, Nicholls G. Validating aminoterminal BNP assays: a word of caution. *Lancet* 1999; 353:1068-1069.
 280. Yu CM, Sanderson JE, Shum IO, Chan S, Yeung LY, Hung YT, Cockram CS, Woo KS. Diastolic dysfunction and natriuretic peptides in systolic

- heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. *Eur Heart J* 1996; 17:1694-1702.
281. Yu SH, Whitworth JA, Kincaid. Smith PS. Malignant hypertension: aetiology and outcome in 83 patients. *Clin Exp Hypertens A*. 1986; 8:1211-1230.
282. Zabalgoitia M, Berning J, Korn MJ, Stoylen A, Nieminen MS, Dahlof B, Devereux RB. Impact of coronary artery disease on left ventricular systolic function and geometry in hypertensive patients with left ventricular hypertrophy (the LIFE Study) *Am J Cardiol*.2001; 88: 646-650.
283. Zolk O, Engmann S, Munzel F, Krajcik R. Chronic cardiotrophin-1 stimulation impairs contractile function reconstituted heart tissue. *Am J Physiol Endocrinol Metab* 2005; 288:e1214-E1221.

APPENDICES